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Hodnocení morfologie obličeje pacientů s orofaciálními rozštěpy v návaznosti na terapeutické postupy

Disertační práce

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Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně s použitím citované literatury. Tato práce ani její podstatná část nebyla předložena k získání jiného či stejného akademického titulu.

V Praze dne 11. dubna 2018 Mgr. Veronika Moslerová

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Poděkování

Ráda bych na tomto místě poděkovala své školitelce doc. Janě Velemínské za vstřícné a trpělivé vedení mé disertační práce a za cenné rady a připomínky po celou dobu mého studia, bez nichž by tato práce nemohla vzniknout.

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Abstrakt

Předkládaná dizertační práce shrnuje výsledky výzkumu zaměřeného na studium kraniofaciální morfologie u pacientů s obličejovými rozštěpovými vadami v návaznosti na terapeutické přístupy (Caganova et al., 2014; Dadáková et al., 2016; Hoffmannova et al., 2016; (Caganova et al., 2014; Dadáková et al., 2016; Hoffmannova et al., 2018; Moslerová et al., 2018). Účinky terapie jedinců s patologickými odchylkami růstu není možné hodnotit bez detailních auxologických studií kontrolních jedinců, jejichž morfologie obličeje, longitudinální změny popř. projevy pohlavního dimorfismu byly hodnoceny na základě obdobné metodologie (Koudelová et al. 2015). Disertační práce tedy byla koncipována jako svazek šesti publikací s obecným syntetickým úvodem do dané problematiky. Dohromady práce zahrnuje probandy širokého věkového spektra od narození do 15 let v celkovém počtu 294 3D faciálních skenů, 36 telerentgenových snímků obličeje, 112 3D skenů sádrových odlitků patra. Při hodnocení převládají metody geometrické morfometrie a mnohorozměrné statistiky.

Stěžejní klinická část disertace se zabývá vlivem dvou typů operativy na růst a vývoj obličeje pacientů s rozštěpy, konkrétně neonatální cheiloplastiky (NCH) a sekundární spongioplastiky (SS). Neonatální cheiloplastika (NCH) je operativa, jejíž vliv byl studován z několika aspektů. NCH je operace defektu rtu prováděná během prvních dvou týdnů života, nejčastěji pak mezi 1. a 7. dnem po narození. Ve dvou studiích se zabýváme hodnocením růstu patra u dětí s kompletním jednostranným rozštěpem rtu, čelisti a patra (cUCLP) a méně závažnou vadou s mostem (UCLP+b) během prvních deseti měsíců života. V tomto období před následující operativou (palatoplastikou) můžeme jasně definovat případné negativní vlivy NCH na růst maxily. Výsledky ukázaly, že patra u dětí po neonatální sutuře prodělávají bez ohledu na rozsah postižení obdobné růstové změny, přičemž patra u kompletních rozštěpů jsou výrazněji formována účinky NCH než patra u jedinců s mostem. K největšímu růstu v tomto období dochází na anteriorních a posteriorních okrajích obou patrových segmentů, přičemž maxila UCLP pacientů vykazuje podobné tendence růstu jako u porovnávaných dat zdravých jedinců. Z našich výsledků vyplývá velmi důležitý poznatek, že neonatální sutura rtu během prvního roku života sama o sobě nelimituje růst horní čelisti na anteriorních koncích a v předozadním směru celkově a během sledovaného období nedochází k zúžení dentoalveolárního oblouku v oblasti mezi špičáky (Hoffmannova et al. 2016, Hoffmannova et al., 2018).

Vliv NCH na morfologii obličeje předškolních dětí s rozštěpovou vadou byl hodnocen na základě tvaru celkového povrchu obličeje. U pacientů s izolovaným rozštěpem rtu (UCL), celkovým jednostranným rozštěpem rtu, čelisti a patra (UCLP) a celkovým oboustranným rozštěpem rtu, čelisti a patra (BCLP) byl sledován vývoj obličeje ve dvou věkových kategoriích a následně porovnáván s věkově odpovídající normou. Odchylky morfologie obličeje v porovnání s normou jsou u všech sledovaných rozštěpových vad nejvíce patrné v oblasti nosu a v místě vzniku vady (*philtrum*), u (UCLP) a (BCLP) je navíc mírně hypoplastická oblast tváří. Nejvíce jsou postiženi BCLP jedinci a odchylky se pouze nesignifikantně zvýrazňují s věkem. Závěry naší studie naznačují, že neonatální cheiloplastika nemá ve věku mezi 3. a 5. rokem života negativní vliv na růst obličeje (Dadáková et al., 2016).

Navazující studie se týkala rozšířeného souboru týchž pacientů, u nichž byla dále sledována asymetrie obličeje, která bývá typickým projevem pacientů především s jednostrannými orofaciálními rozštěpy a bývá akcentována právě s ohledem na chirurgický zákrok. Z výsledků vyplývá, že jednostranné vady (UCL, UCLP) vykazují asymetrii zejména primárně postižené nasolabiální oblasti, u UCLP pacientů asymetrie zasahuje i laterálnější oblast tváří. Nečekané bylo zjištění, že BCLP pacienti, přestože mají defekt horního rtu oboustranně, vykazují souhlasně s UCL a UCLP pozitivní odchylky od symetrie v oblasti horního rtu vlevo. V ostatních oblastech se asymetrie BCLP od UCLP liší, ale v porovnání s jednostrannými vadami je asymetrie méně výrazná a má spíše charakter asymetrie kontrolních souborů. Kromě bukální oblasti se asymetrie s věkem nezvýrazňuje (Moslerová et al., 2018).

Sekundární spongioplastika je zákrok spočívající ve vyplnění defektu horní čelisti drobnými spongiózními štěpy a provádí se v období nejčastěji mezi 7. a 9. rokem, v závislosti na prořezávání stálých špičáků. Hlavním cílem operativy je doplnění chybějící kosti horního alveolárního oblouku a umožnění prořezání trvalého špičáku v místě původního rozštěpu. V naší studii byl sledován efekt této terapie na vývoj obličeje v období mezi 10. a 15. rokem věku, které je v ontogenezi splanchnokrania pacientů s orofaciálními rozštěpy kritické. Z výsledků vyplývá, že vývoj obličeje chlapců operovaných metodou SS probíhá uspokojivěji než v případě PP jedinců. Pacienti s SS měli v porovnání s předchozí operativou celkově konvexnější profil, výraznější prominenci nosu a méně poškozené vertikální vztahy mezi oběma čelistmi (Cagáňová et al., 2014).

Stěžejní klinická část je doplněna auxologickou studií založenou na longitudinálním sledování morfologie obličeje zdravých jedinců ve věku pubertálního spurtu. Období adolescence je z hlediska studia patologického vývoje rozštěpových pacientů velmi důležité, neboť právě v tomto období je popisována nedostatečnost růstu střední části obličeje a zhoršení mezičelistních vztahů. Metodologie, podobně jako u většiny studií předchozí části disertace, je založena na hodnocení variability i průměrné formy/tvaru obličeje na základě 3D virtuálních povrchových faciálních modelů pokročilými metodami geometrické morfometrie. Studie Koudelová et al. (2015) přinesla z klinického hlediska cenný poznatek, že mezi 12. a 15. rokem nebyl prokázán pohlavní dimorfismus tvaru obličeje po odškálování jeho velikosti. Pohlavní dimorfismus formy obličeje byl signifikantně odlišný od 14 let věku.

Klíčová slova

Neonatální cheiloplastika, sekundární spongioplastika, rozštěp, růst patra, morfologie obličeje, asymetrie obličeje, 3D geometrická morfometrie, klasická morfometrie, pohlavní dimorfismus

Abstract

The presented thesis summarizes the results of research on craniofacial morphology in patients with facial cleft defects in relation to therapeutic approaches (Caganova et al., 2014; Dadáková et al., 2016; Hoffmannova et al., 2016; Hoffmannova et al., 2018; Moslerová et al., 2018). The effect of therapy in individuals with pathological growth disorders cannot be evaluated without detailed auxological studies of control subjects whose facial morphology, longitudinal changes, or manifestations of sexual dimorphism were evaluated upon similar methodology (Koudelová et al. 2015). Therefore, the thesis was conceived as a volume of six publications complemented with a general synthetic introduction into the area of study. Together, the thesis includes probands in a broad age spectrum from birth to 15 years with a total of 294 facial 3D scans, 36 tele-X-ray face images, 3D scans of 112 gypsum palate castings. The methods of geometric morphometry and multidimensional statistics prevail in the assessment.

The main clinical part of the thesis deals with the influence of two types of surgery on the facial growth and development of patients with cleft palate, namely secondary spongioplasty (SS) and neonatal cheiloplasty (NCH). Neonatal cheiloplasty (NCH) is the surgery whose effects were studied from several angles. NCH is a lip defect surgery performed during the first two weeks of life, most often between 1 and 7 days after birth. In two of our studies we deal with assessment of palate growth in children with complete unilateral cleft lip, jaw and palate (cUCLP) and a less severe defect of the bridge (UCLP+b) during the first ten months of life. In this period before the next surgery (palatoplasty) we can clearly identify any possible negative effects of NCH on the growth of the maxilla. The results showed that the palate in children after neonatal suture underwent similar growth changes regardless of the extent of the impairment, while palates in case of complete clefts were significantly more affected by the NCH than the palate in the individuals with a bridge. The largest growth in this period occurs at the anterior and posterior margins of both palate segments, with the maxilla in UCLP patients exhibiting similar growth tendencies as compared with data from healthy individuals. Our results suggest a very important lesson that neonatal suture of the lip during the first year of life itself does not limit the growth of the maxilla at the anterior ends and in the anteroposterior direction overall and during the observed period it does not lead to narrowing of the dentoalveolar arc in the space between the canines (Hoffmannova et al. 2016, Hoffmannova et al., 2018).

The impact of NCH on facial morphology of pre-school children with a cleft defect was evaluated based on the shape of the overall face surface. In patients with isolated cleft lip (UCL), unilateral complete cleft lip, jaw and palate (UCLP) and bilateral complete cleft lip, jaw and palate (BCLP) there was observed the development of face in two age categories and then compared with the corresponding age standard. In all the cleft defects, deviations of facial morphology, as compared to the standard, were the most evident in the nasal area and in the place of origin of the defect (*philtrum*), while in (UCLP) and (BCLP) there was also slightly hypoplastic buccal area. The BCLP individuals were the most severely affected and their deviations become only non-significantly more pronounced with age. The most important conclusion of the study is the finding that neonatal cheiloplasty does not have negative effect on the growth of the face between the 3rd and 5th year of life (Dadáková et al., 2016).

The follow-up study studied an extended set of the same patients whose facial asymmetry was observed, being a typical manifestation in patients primarily with unilateral orofacial clefts and is usually accentuated due to the surgical procedure. The results indicate that unilateral defects (UCL, UCLP) possess asymmetry especially in the primarily affected nasolabial area, while in UCLP patients the asymmetry affects also the more lateral facial region. It was unexpected to discover that BCLP patients, although having an upper lip defect on both sides, showed positive symmetry deviations, similar to UCL and UCLP, in the upper lip on the left. In other areas, BCLP's asymmetry varies from UCLP, but compared to unilateral defects the asymmetry was less pronounced and it may be considered as only an asymmetry of a control set. Apart from the buccal area, the asymmetry does not become more pronounced with age (Moslerová et al., 2018).

Secondary spongioplasty is an operation consisting in filling the upper jaw defect with small spongiose grafts and is performed most commonly between the seventh and ninth year of age, depending on the emergence of permanent canine teeth. The main objective of the surgery is to supplement the missing bones of the upper alveolar arc and to enable the emergence of a permanent canine tooth in place of the original cleft defect. In our study we observed the effects of this therapy on the development in face between 10 and 15 years of age, which is highly critical age in the ontogenesis of the splanchnocranium of patients with orofacial clefts. The results reveal that the alveolus defect (SS) remedial method has a very positive impact on the

formation of the patient's face. When compared with previous surgery type, the profile of patients with SS was more convex, with more pronounced nose and less damaged vertical relationship between the two jaws (Cagáňová et al., 2014).

The main clinical part is complemented with an auxological study based on longitudinal observation of facial morphology in healthy individuals at the age of puberty spurt. Adolescence is very important, as concerns the study of cleft patient pathological development because it is this period when the insufficient growth in the middle part of the face and the deterioration of the intermaxillary relationships are described. The methodology, like in most previous studies, was based on the evaluation of variability and average form/shape of the face studied in virtual 3D facial surface models, using advanced methods of geometric morphometry. A study by Koudelová et al. (2015) provided an observation, very valuable from the clinical point of view, that between the 12^{th} and 15^{th} age no sexual dimorphism in the facial shape was proven after scaling to size. Sexual dimorphism in facial morphology was significantly different from the age of 14.

Key words

Neonatal cheiloplasty, secondary alveolar bone rafting, cleft, palate growth, facial morphology, facial asymmetry, 3-D geometric morphometry, classical morphometry, facial sexual dimorphism

Použité zkratky

2D	dvojrozměrný
3D	trojrozměrný
BCLP	oboustranný/bilaterální rozštěp rtu, čelisti a patra
BMP	kostní morfogenetický protein
CBCT/CT	Cone Beam výpočetní tomografie/výpočetní tomografie
CLP	kompletní jednostranný/oboustranný rozštěp rtu, čelisti a patra
CP	rozštěp patra
CPD-DCA	coherent point drift – dense correspondence analýza
cUCLP	kompletní jednostranný rozštěp rtu, čelisti a patra
FGF	fibroblastový růstový faktor
K*	kontrolní jedinci- srovnávací soubor
m	měsíc
n	počet jedinců
NCH	neonatální cheiloplastika
PC	hlavní komponenta
PCA	analýza hlavních komponent
PCH	pozdní cheiloplastika
PCH*	pozdní cheiloplastika – srovnávací soubor
PO	primární osteoplastika
PP	primární periosteoplastika
r	rok
Shh	sonic hedgehog
SS	sekundární spongioplastika
teleRtg	telerentgenografie
TIMP-1	tkáňový inhibitor metaloproteinázy-1
UCL (CL)	jednostranný/unilaterální rozštěp rtu
UCLP	jednostranný/unilaterální rozštěp rtu, čelisti a patra
UCLP+b	jednostranný rozštěp rtu, čelisti a patra s mostem
ÚZIS	Ústav zdravotnických informací a statistiky ČR
VVV	vrozená vývojová vada

Obsah

1 Teoretický úvod

Narození dítěte s vrozenou vývojovou vadou (VVV) je pro rodinu vždy velká zátěž a cílem klinických odborníků je co možná nejvíce zmírnit dopad této vady jak na nositele samotného, tak na jeho nejbližší okolí.

Za vrozenou vývojovou vadu je považována odchylka od normálního prenatálního vývoje, která vzniká jak na podkladě genetickém, tak v důsledku působení vnějších faktorů či jejich vzájemnou kombinací. VVV se může vyskytovat buď izolovaně, nebo může být spolu s dalšími malformacemi součástí syndromické jednotky. Celosvětově se prevalence VVV udává v rozmezí 2-3% (Corsello and Giuffrè, 2012), na Evropském kontinentu je VVV popisována přibližně u 2,4% narozených dětí (Dolk et al., 2010). Dle Ústavu zdravotnických informací a statistiky ČR (ÚZIS) se v České republice od roku 2000 pohybuje míra prevalence všech VVV v rozmezí 3,6 až 4,8 % narozených dětí, přičemž obličejové rozštěpové vady mají na tomto množství značný podíl. Z celkového počtu VVV tvoří rozštěpové vady 3,9 % a jsou pátou nejčastější vrozenou vadou s incidencí pohybující se okolo 1,6 na 1000 živě narozených dětí (ÚZIS, 2014).

Z výše uvedeného je tedy zřejmé, že rozštěpové vady a VVV obecně nejsou jevem v žádném případě ojedinělým a důkladný výzkum týkající se jak vad samotných, tak jejich terapie, bude i nadále výzvou pro lékaře, vědce a další klinické pracovníky.

1.1 Obecný úvod do problematiky rozštěpových vad

Vývoj rtu a patra představuje komplex na sebe přesně navazujících událostí, které vyžadují úzkou koordinaci migrace, růstu, diferenciace a apoptózy zúčastněných buněk (Mossey et al., 2009). Lidský obličej se začíná vyvíjet ve čtvrtém týdnu embryogeneze migrací buněk neurální lišty, jejich spojením s buňkami mezodermu a založením faciálních primordií (Schutte and Murray, 1999; Jiang, 2006; Mossey et al., 2009) za následného vzniku párových maxilárních a mandibulárních výběžků a nepárového výběžku frontonazálního, ze kterého se diferencují párové mediální a laterální nazální výběžky (Wyszynski, 2002; Jiang, 2006). V dalších týdnech dochází k postupné fúzi těchto výběžků, což je klíčovým momentem při správné formaci kraniofaciálních struktur. Esenciální roli hrají při tomto procesu FGF, BMP a Shh signalizace (Mossey al., 2009; Burg et al., 2016; Xavier et al., 2016). Pokud je z nějakého důvodu proces splynutí v kritické periodě (4. – 6. tt) narušen, vzniká obličejový rozštěp (Moore et al.,

2008). Nejlehčí formou je izolovaný rozštěp rtu, vyskytující se v různém stupni závažnosti od zářezu do retní červeně až po úplný rozštěp rtu (Dušková et al., 2007; Campbell et al., 2017), přičemž závažnost má vliv na finální vzhled rtu a nosu po operaci (Campbell et al., 2017). Závažnějším postižením je rozštěp rtu a čelisti, kdy je kromě rtu postižena i alveolární oblast (Jelínek et al., 1983). Oba výše jmenované typy rozštěpu se mohou vyskytovat ve formě jednostranné či oboustranné (Dušková et al., 2007). Vývoj patra začíná o něco později, koncem pátého týdne gestace a bývá ukončen během týdne dvanáctého, s kritickou periodou mezi šestým a devátým týdnem. Důvodem vzniku rozštěpu patra je nesplynutí patrových plotének během procesu horizontalizace z původně vertikální polohy podél jazyka (Bernheim et al., 2006; Moore et al., 2008; Mossey et al., 2009). Důvodem může být například nedostatečný růst dolní čelisti nebo hypoplazie plotének samotných (Peterka, 2005). Výsledkem může být rozštěp měkkého patra, submukózní rozštěp patra nebo nejzávažnější forma – rozštěp měkkého i tvrdého patra (Jelínek et al., 1983; Schutte and Murray, 1999; Burg et al., 2016). I přes naprosto odlišný embryonální vývoj se rozštěp rtu a rozštěp patra často vyskytují spolu ve formě kompletního jedno- či oboustranného rozštěpu rtu, čelisti a patra (Jelínek et al., 1983; Bernheim et al., 2006).

Příčinu vzniku rozštěpových vad nelze ze 70% přesně určit a jedná se zřejmě o kombinaci více slabších genetických a epigenetických faktorů, tzv. faktoriální komplex (Peterka, 2005). Přibližně z 20% nalézáme na pozadí vzniku rozštěpu genetickou příčinu. V současné době je známa řada genů, která se podílí na řízení a regulaci kraniofaciálního vývoje a hrají významnou úlohu při vzniku nesyndromického rozštěpu (Vanderas, 1987; Wyszynski, 2002; Bernheim et al., 2006; Rahimov et al., 2012; Luijsterburg et al., 2014). Rozštěpová vada se však může vyskytovat i jako součást určitého genetického syndromu (Schutte and Murray, 1999), přičemž syndromů, zahrnujících rozštěpovou vadu jako jeden z příznaků, je v současnosti dle London Medical Database popsáno více než 700 (Winter and Baraitser, 2010). Z vnějších faktorů, které samy stačí na vyvolání vady, jsou to např. cytostatika, imunosupresiva, antiepileptika, vitamín A či záření, popřípadě jde o kombinaci více slabších faktorů současně (infekci, horečku, léčbu antibiotiky) (Peterka, 2008; Hill and Finnell, 2010).

Rozštěpová vada nezpůsobuje morfologické odchylky pouze v oblasti defektu, ale ovlivňuje růst i dalších kraniofaciálních struktur. Na vrozenou vadu navazuje hypoplazie všech tkání ve střední části obličeje (Dušková et al., 2007), přičemž maxila

je zejména z důvodu zúžení alveolárního oblouku a celkové hypoplazie považována za vůbec nejproblematičtější oblast (Capelozza et al., 1996; Lee et al., 2014; Fariña et al., 2018). Dle Šmahela a Brejchy nalézáme u pacientů s orofaciálními rozštěpy šest základních skeletálních odchylek, které se postupně vyvíjejí až do ukončení růstu lebečních struktur. Pět odchylek se týká horní čelisti a řadíme sem zmenšení horní výšky obličeje, zmenšení délky maxily a zúžení horního dentoalveolárního oblouku (vyjma UCL), dentoalveolární retroinklinaci a posun maxily posteriorně oproti bazi lební. Poslední odchylka se týká dolní čelisti, konkrétně redukci délky větve a těla mandibuly (Smahel and Brejcha, 1983). Kromě hypoplazie obličejových struktur je u jedinců s rozštěpovou vadou téměř vždy přítomna určitá míra asymetrie a to zejména v oblasti nasomaxilárního komplexu (Kyrkanides et al., 1995; Bugaighis et al., 2010). Nejvíce dominující asymetrie měkkých tkání je popisována v oblasti rtů a nosu, která souvisí s jizvou v oblasti chirurgického zákroku a asymetrií skeletálního podkladu (Lo, 2006; Bugaighis et al., 2014a; Al-Rudainy et al., 2018).

Cílem celé skupiny specialistů je během vývoje jedince od narození do dospělosti co nejúspěšněji minimalizovat negativní vliv vady, zejména odchylek morfologie obličeje, funkčnosti narušených struktur, vývoje řeči či sociálně-psychologických aspektů. Kompletní léčebný protokol zahrnuje řadu chirurgických a ortodontických zákroků, stejně tak jako intervenci foniatra, logopeda či psychologa. Neméně důležitou úlohu hraje pediatr a na vyšetřování se podílí také genetik a antropolog. Hlavní úlohou antropologa je identifikace odchylek skeletu a měkkých tkání obličeje porovnáním s normou, sledování vývoje jednotlivých odchylek v čase a hodnocení účinků terapie od chirurgických zákroků, přes ortodontickou léčbu až po protetiku.

1.2 Studované operační metody

První písemná zmínka o operaci rtu pochází z roku 390 n.l. z Číny (Sandberg et al., 2002). Zmínky o chirurgickém řešení rozštěpů na Evropském kontinentu nacházíme z období kolem roku 950 n.l. V 16. století se začaly vyvíjet první typy patrových obturátorů a v 18. století dochází k mohutnému rozvoji nástrojů a technik k řešení defektu rtu a patra. V 19. století se začínají rozštěpové vady operovat i na americkém kontinentu (Dušková et al., 2007). Na našem území se měnil přístup k léčbě rozštěpových pacientů v několika poválečných etapách. Nejdříve se jednalo

o nekomplexní ortodontickou léčbu bez chirurgické úpravy alveolárního výběžku, ret operován metodou dle Veau ve věku mezi 7. a 9. měsícem. Po roce 1957 se péče centralizovala, alveolární výběžek nicméně stále nebyl rekonstruován. V druhé polovině šedesátých let byla pro rekonstrukci alveolu zavedena metoda primární osteoplastiky (PO) a v ortodoncii se začaly využívat fixní aparáty. V první polovině sedmdesátých let byla PO nahrazena primární periosteoplastikou (PP). V osmdesátých letech byla léčba doplněna o repozici nosního septa a ret se začíná operovat metodou dle Tennison-Randalla. V devadesátých letech se začala pro řešení defektu alveolu používat metoda sekundární spongioplastiky (SS). Patro bylo po celou dobu operováno shodně metodou retropozice s faryngofixací, přičemž načasování operace bylo posunuto do výrazně vyššího věku než dnes, mezi 4. - 6. rokem života (Smahel et al., 1998). V posledních letech je ret standardně operován v průměru okolo 3. měsíce (mezi 3. až 6. měsícem ve světě) a patro kolem 9. měsíce věku dítěte (Borský, 2014). V současnosti je jako alternativa prováděna operace rtu v novorozeneckém věku během prvních 14 dní života tzv. neonatální cheiloplastikou (NCH) (Borský, 2014; Košková et al., 2016).

Neonatální cheiloplastika

První operací, kterou pacienti s rozštěpovou vadou podstupují, je sutura rtu. V ideálním případě by se mělo dosáhnout přiblížení mediální a laterální části rtu tak, aby nedošlo ke ztrátě přirozených anatomických struktur. Žádoucí je odstranit ty okrajové části, které by bránily vytvoření ideální linie horního rtu společně s doplněním tkáně do ideální délky a dosažením správné výšky rtu odstraněním tkáně nadbytečné. Jizva by měla kopírovat přirozené linie s ohledem na anatomii oronazální oblasti. Mělo by být dosaženo správné funkce svalu *m.orbicularis oris*, obě nostrily by měly mít po obvodu stejný tvar a obě nosní křídla by měla být z předního pohledu symetrická (Fisher and Sommerlad, 2011).

Neonatální cheiloplastika (NCH) je stále častěji využívaná alternativa k cheiloplastice prováděné v pozdějším věku (PCH), nejčastěji mezi 3. a 6. měsícem života (Wyszynski, 2002; Kobus and Kobus-Zaleśna, 2014). První studie, popisující NCH jako možnou variantu ke standardnímu řešení rozštěpu rtu po třetím měsíci života, se objevují již v první polovině minulého století. Blair & Brown (1931) ve své práci detailně popisují metody chirurgického řešení rozštěpu rtu, jež spolu s korekcí deformity nosu ve snaze dosáhnout co nejvyšší možné symetrie, standardně provádějí v novorozeneckém věku, pokud možno již v prvních 24 hodinách po narození. Jedním

z důvodů časné operativy je předpoklad, že novorozenec je stále ještě vybaven jakousi „imunitou“ vůči šoku z chirurgického zákroku, který je bezpochyby přítomen během porodu. Hlavní výhody ovšem spatřují v dalších benefitech pro pacienta: „Technika operace v tomto ranném věku je náročná, nicméně výhody pro matku a dítě převažují nad nevýhodami pro chirurga“. Po 48 hodinách po operaci může být dítě již normálně kojeno či krmeno z lahve (Blair and Brown, 1931). Straith et al. (1955) ve své práci týkající se chirurgických zákroků v obličeji u novorozenců v lokální anestezii, prezentuje širokou skupinu pacientů s různou závažností rozštěpu, operovaných během prvních 28 dní života, často 7. den po narození. Zákroky jsou prováděny nikoliv v celkové, nýbrž v lokální anestezii z důvodu nižšího rizika pro novorozence (Straith et al., 1955). Tento argument bude u části operatérů v dalších letech a víceméně dodnes jedním z důvodů, proč suturu rtu odkládat do pozdějšího věku. Další početné soubory pacientů podstoupivších NCH zmiňují práce z 80. a 90. let minulého století. Shodují se na minimálním výskytu komplikací, dobrém estetickém a funkčním efektu pro dítě a současně pozitivním vlivu na matku/rodinu (Bromley et al., 1983; Weatherley-White et al., 1987; Freedlander et al., 1990). Weatherley-White et al. (1987) hodnotí NCH s následným kojením jako ideální management dítěte s rozštěpovou vadou (Weatherley-White et al., 1987).

Růst obličeje pacientů s rozštěpovou vadou je ovlivněn nejen prodělanými operacemi, ale i následnou ortodontickou péčí (Kuijpers-Jagtman and Long, 2000). Odlišit vliv jednotlivých operací na utváření kraniofaciální oblasti není jednoduchý. Vzhledem k tomu, že je potřeba uzavřít jak rozštěp rtu a čelisti, tak i rozštěp patra, není z etického hlediska možné studovat vliv jednotlivých operací na randomizovaných kontrolních skupinách (Kuijpers-Jagtman and Long, 2000). Nedostatečný růst maxily, a s tím související retruze a oploštění střední části obličeje, byl dlouho připisován na vrub palatoplastiky (Hagerty and Hill, 1963; Kuijpers-Jagtman and Long, 2000). Hagerty a kolektiv však přisuzují zásadní vliv na redukci růstu maxily v předozadním směru cheiloplastice, v důsledku tlaku na anteriorní část dentálního oblouku, který je dále přenášen na maxilární segmenty (Hagerty and Hill, 1963). Tuto teorii podporují i výsledky na zvířecích modelech, kde je po operaci rtu v porovnání s kontrolou prokázána signifikantní inhibice předozadního růstu horní čelisti. Zároveň autoři popisují výraznou maxilární i mandibulární asymetrii (Kremenak, 1967; Bardach and Eisbach, 1977; Eisbach et al., 1978; Bardach, 1990). Zásadní roli na růst horní čelisti přisuzuje v polovině devadesátých let cheiloplastice i tým profesora Capellozzy, kterým

se podařilo shromáždit dospělé muže s kompletním rozštěpem rtu a patra, a to jak skupinu neoperovaných, tak skupinu, která podstoupila pouze cheiloplastiku a nakonec jedince odoperované cheilo- i palatoplastikou. Mezi kompletně a pouze cheiloplastikou odoperovanými jedinci nenalézali významné rozdíly, nicméně tyto dvě skupiny v porovnání s neoperovanými jedinci vykazovaly signifikantní retruzi maxily. Autoři tedy považují za zásadní věnovat pozornost zejména modifikaci protokolu primární sutury rtu, nikoliv protokolu palatoplastiky (Capelozza et al., 1996). Tento argument je zásadní vzhledem k tomu, že růst obličejových struktur se významně liší v souvislosti s použitým operačním protokolem cheilopastiky (Bardach and Eisbach, 1977; Shi and Losee, 2014).

O nutnosti odoperování defektu rtu není sporu, hlavní diskuze se však vedou ohledně jeho načasování. Jako hlavní argument pro odložení operace do pozdějšího věku jsou udávána rizika spojená s anestezií u novorozenců, kdy je většina orgánů nezralá a je teoretické riziko návratu fetálního oběhu. Autoři také poukazují na fakt, že během krátké doby mezi narozením a operací není možno stoprocentně vyloučit přítomnost dalších VVV (Straith et al., 1955; Wilhelmsen and Musgrave, 1966; Drayton and Skidmore, 1987; Van Boven et al., 1993). Cohen et al. (1990) ve své práci porovnává výskyt pooperačních komplikací v souvislosti s anestezií u souboru téměř 30.000 jedinců, přičemž nejvyšší míru komplikací zaznamenává u dětí mladších jednoho měsíce. Ze studie však vyplývá, že většina takto časně operovaných dětí podstoupila anestezii z důvodu nutnosti kardiologické či vaskulární operace, tedy okolností, které samy o sobě bezprostředně ohrožují pacienta na životě (Cohen et al., 1990). Van Boven et al. (1993) uvádí výskyt komplikací u několika případů časně operovaných novorozenců s rozštěpem, přičemž předoperační důkladné sonografické vyšetření potvrzuje pouze u 1/3 případů. V závěru dodává, že NCH shledává jako bezpečnou metodu u novorozenců, kteří jsou před operací řádně vyšetřeni v souvislosti s možným kardiologickým defektem a anestezie je provedena zkušeným dětským anesteziologem (Van Boven et al., 1993). Z výše uvedených důvodů je vždy nepostradatelná úloha neonatologa, který před zákrokem provede pečlivý předoperační screening, zejména z důvodu detekce vrozených vad srdce, centrálního nervového systému a trávicího traktu. Neméně důležité je také vyloučení poruch srážlivosti či případných hematologických onemocnění. V dnešní době pokročilých vyšetřovacích metod, není problém novorozeného pacienta tímto způsobem na časný zákrok připravit. Anestezii by měl vždy podávat zkušený dětský anesteziolog a pracoviště by mělo být

vybavené k péči o novorozence. Při splnění těchto podmínek benefit úpravy rtu převažuje rizika anestezie (Borsky, 2014). Časná operativa, co se týče rizik anestezie, má své zastánce a publikované pozitivní výsledky již dlouhodobě. Buntain et al. (1972) tvrdí, že během prvních 48 hodin je novorozenec v ideálním stavu pro podstoupení velkého chirurgického zákroku v celkové anestezii. Je ve stavu hypervolémie a polycytémie, má zvýšenou hladinu kortikoidů v krvi, což je výhodné pro boj se stresovou situací (Buntain et al, 1972 cit. podle Desai 1997, s. 11). V souladu s tím další autoři uvádějí nulovou mortalitu a minimální morbiditu u pacientů s NCH v souvislosti s anestezií (v minimálním počtu případů je uváděna hypoxémie, hypoxie), zanedbatelnou potřebu krevní transfúze či opětovné reintubace. Pokud už se komplikace vyskytly, neměly dlouhodobé následky (Akin et al. 1991; Borsky et al. 2012; Desai 1997; Freedlander et al. 1990; Galinier et al. 2008; Harris et al. 2010; Mcheik et al. 2006; Stephens et al. 1997; Weatherley-White et al. 1987). Bromley et al. srovnal soubory NCH a PCH a co se týče komplikací v souvislosti s anestezií, nachází je pouze u 3,2 % případů (aspirační pneumonie, respirační deprese) a to ve dvou případech u NCH a třech případech u PCH (Bromley et al., 1983). Recentní práce autorů Lee et al. (2017) zhodnotila data všech pacientů, kteří podstoupili cheiloplastiku během prvního roku života mezi roky 2004-2010 napříč Spojenými Státy a uvádějí až 15krát vyšší riziko rozvoje komplikací u neonatálně operovaných dětí. Nicméně jejich soubor obsahuje necelé dvě stovky NCH pacientů z celkových více než 10 000 za celé sedmileté období, tzn. 1,9%. Z tohoto poměru a celkové délky hospitalizace NCH pacientů (v průměru 19 dní) se můžeme domnívat, že NCH zde v této době nebyla rutinně prováděnou operací a častější komplikace mohou být v důsledku nedostatku zkušeností s touto operativou. Navíc autoři neuvádějí typ komplikace a chybí i další podstatné informace.

Negativem NCH může být menší velikost tkání a tím pádem složitější práce pro plastického chirurga (Blair and Brown, 1931; Weatherley-White et al., 1987; Akin et al., 1991), nicméně chirurgové operující touto metodou, vidí tento fakt jako jediný zápor operativy. Navíc, při odložení operace do pozdějšího věku, sání produkuje sílu, která během tohoto období u jednostranných rozštěpů tlačí rozštěpenou čelist dopředu a u oboustranných vytlačuje dopředu celou premaxilu. V případě NCH hraje ret roli svěrače a vytváří souvislý tlak na frontální segment maxily, což vede k brzké úpravě její anatomie, zatímco jazyk tlačí na patro, díky čemuž je tvarován dentální oblouk a zároveň dochází k uzavírání alveolárního rozštěpu a kontaktu obou segmentů (Akin

et al., 1991; Desai, 1997; Valentová-Strenáčiková and Malina, 2016). Valentová-Strenáčiková & Malina popisují u pacientů po NCH rapidní zmenšení velikosti defektu alveolu během prvních třech měsíců života, dále je pokles kontinuální. Oproti tomu u PCH popisují mírný nárůst velikosti defektu v období před operací, který se začíná snižovat až po zákroku, přičemž rozdíl oproti NCH zůstává signifikantní (Valentová-Strenáčiková and Malina, 2016). Podobné, ale ještě progresivnější přiblížení obou segmentů popisuje Akin et al. (1991). Během prvních 15 dní se u jejich souboru pacientů zmenšuje rozštěpová štěrbina na 1-2 mm, ke vzájemnému kontaktu dochází během 3. měsíce u UCLP a během 10. měsíce u BCLP pacientů. Příliš rychlé přiblížení segmentů však může mít negativní vliv na růst horní čelisti v předozadním směru. Borský et al. (2012) se snaží vyhnout příliš časnému kontaktu segmentů modifikací operačního protokolu a eliminací tlaku zjizvené tkáně na jednotlivé segmenty. U jedinců operovaných ve třech měsících či později, popisuje (Akin et al., 1991) zmenšení rozštěpové štěrbiny na 2-3 mm mezi 5. a 8. měsícem a uzavření defektu ve 12. měsíci u jednostranných vad, u oboustranných pak ke spontánnímu spojení segmentů nedochází a je potřeba revizního zákroku. Valentová-Strenáčiková & Malina (2016) u NCH dále popisují kontinuální nárůst anteriorní oblasti nepostiženého segmentu a vylepšování vzájemného postavení obou segmentů, zatímco u PCH je nárůst nesouvislý a postavení segmentů se začíná vylepšovat až po operaci. Formující efekt NCH na frontální segment se současným nárůstem segmentů na anteriorních i posteriorních okrajích je sledován ve studii Hoffmannova et al. 2016 a Hoffmannova et al. 2018, přičemž růstový trend během prvních deseti měsíců je u UCLP pacientů srovnatelný s růstem zdravých kontrol. Celková délka patra u UCLP pacientů ještě před suturou rtu je popisována kratší než u zdravých jedinců, naproti tomu šířka dentoalveolárního oblouku charakterizovaná vzdáleností mezi špičáky a prvními moláry je u pacientů s UCLP vyšší (Kramer et al., 1994; Hoffmannova et al., 2016). Z řady studií vyplývá, že se vzdálenost mezi řezáky po cheiloplastice u pacientů operovaných pozdní suturou snižuje (Wada and Miyazaki, 1975; Kramer et al., 1994; Honda et al., 1995; Huang et al., 2002). Studie Hoffmannova et al. 2016 a Hoffmannova et al. 2018 nepopisuje u UCLP pacientů během prvního roku života pokles tohoto parametru a růst pacientů má tak více charakter růstu zdravých jedinců. Posteriorní šířka dentoalveolárního oblouku je u UCLP pacientů zpočátku vyšší než u kontrol a dále se během růstu zvyšuje jak u pacientů s NCH, tak u pacientů s PCH a trend je v souladu

s kontrolami (Wada and Miyazaki, 1975; Kramer et al., 1994; Honda et al., 1995; Hoffmannova et al., 2016; Hoffmannova et al., 2018).

Za výrazně pozitivní důsledek časné operativy je pokládána možnost kojení, která přináší nutriční a imunologické benefity pro dítě (Cohen et al., 1992). Blair & Brown (1931) tvrdí, že již 48 hodin po zákroku, je možné dítě kojit či krmit z lahve. Desai (1997) uvádí, že většina dětí odoperovaných NCH se vrací k normálnímu stravovacímu režimu (kojení, krmení lahví) před propuštěním do domácí péče. Podobné výsledky dokládá také Harris et al. (2010), kde bylo u více než poloviny pacientů před opuštěním porodnice úspěšně zahájeno kojení. Weatherley-White et al. (1987) ve své studii předkládají hned několik pozitiv, týkajících se NCH a ve spojitosti s krmením. Přechod z intravenózní na orální výživu je u jimi sledovaných dětí rychlejší, váhové přírůstky popisované u kojených dětí jsou výraznější než u nekojených a celkově se jeví příznivě. Autoři navíc nenacházejí signifikantní rozdíly v estetické kvalitě jizev u časně operovaných kojených dětí v porovnání s pozdně operovanými dětmi. Cohen et al. (1992) také nenalézají rozdíly v hojení a ve finálním vzhledu mezi dětmi kojenými či krmenými lahví a dětmi krmenými nasogastrickou sondou bezprostředně po časné sutuře. Negativní vliv sání nebyl popsán ani u dětí po PCH, kde autoři porovnávali hojení jizvy u dětí krmených lahví s dětmi krmenými lžičkou (Assuncao et al., 2005). Pro časnou operativu může nahrávat také fakt, že sání a krmení dětí, zejména v případech větší závažnosti vady, je insuficientí a tím pádem může být příjem potravy nedostačující (Akin et al., 1991; Grow and Lehman, 2002; Robin et al., 2006; Amstalden-Mendes et al., 2007; Gil-da-Silva-Lopes et al., 2013). V některých případech pozdní operativy je u dětí v období před zákrokem popisováno významné neprospívání (Akin et al., 1991; Mzezewa et al., 2014).

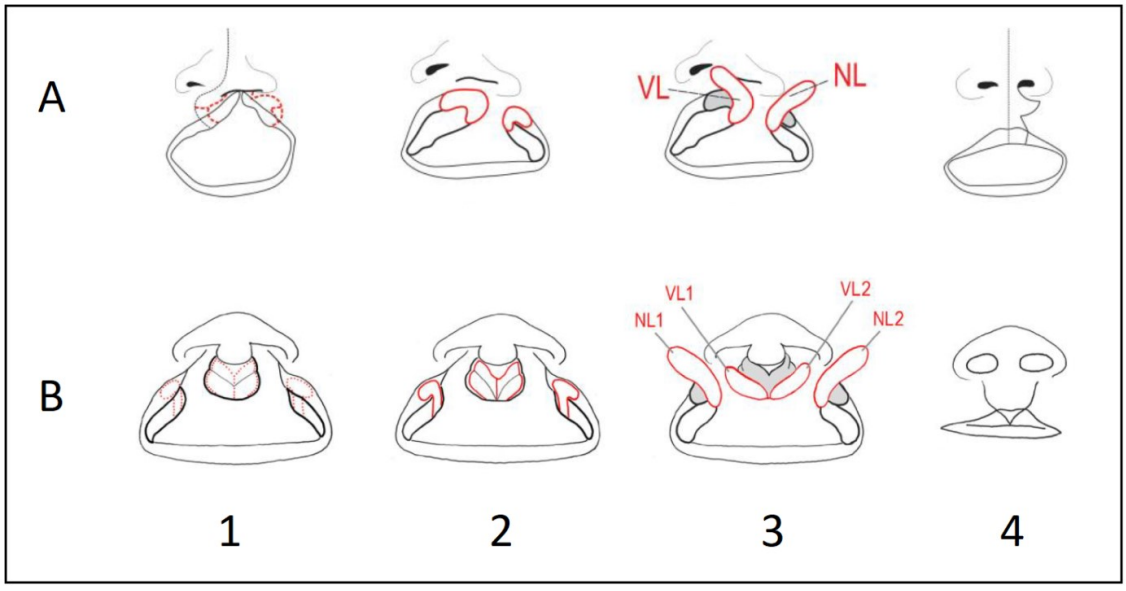
Možnost kojit své dítě, má výrazně pozitivní psychologický vliv na matku (Cohen et al., 1992). Pozitivně na psychiku matky a zbytku rodinu působí také fakt, že si domů z porodnice odvážejí normálně vypadající miminko a míra stresu z vrozené vady a následné náročné péče se tím zmírňuje (Akin et al. 1991; Blair & Brown 1931; Borsky et al. 2012; Borský et al. 2007; Bromley et al. 1983; Calteux et al. 2013; Coolen et al. 2010; Goodacre et al. 2004; Weatherley-White et al. 1987). Galinier et al. (2008) a Mcheik et al. (2006) považují kromě jiných uspokojivých výsledků, pozitivní psychologický vliv na rodinu jako jeden z největších přínosů NCH.

Jedním ze zásadních argumentů pro časnou operativu je také hojení jizvy a finální estetiký výsledek. Uvádí se, že hojení pooperačních ran v novorozeneckém

věku má v porovnáním s odhojování jizev v pozdějším věku lepší prognózu. Důvodem je tzv. fetální vzorec hojení (Adzick & Lorenz 1994; Longaker et al. 1994; Lorenz et al. 1992), který může přetrvávat krátce po narození (Lorenz et al., 1992; Adzick and Lorenz, 1994). Fetální hojení je umožněno díky unikátním fetálním fibroblastům, které rychleji produkují a ukládají komponenty extracelulární matrix za produkce nové tkáně spíše než jizvy (Adzick and Lorenz, 1994). Izolací buněčných populací keratinocytů a fibroblastů z reziduálních tkání pacientů po NCH, byly v kultuře keratinocytů nalezeny populace pozoruhodně malých buněk s markery pro málo exprimovaný keratin 8 a 19. Tyto buněčné populace nebyly u dětí staršího věku nalezeny. Fibroblasty novorozenců se lišily především v expresi proteinu nestinu, který souvisí s proliferačním a diferenciačním potenciálem buňky a významně klesá s věkem. Celkově lze říci, že keratinocyty a fibroblasty novorozenců se signifikantně lišily od buněk získaných od starších kojenců a mohou mít vliv na sníženou tvorbu jizev u chirurgických zákroků prováděných časně po narození (Krejčí et al., 2015). Blaha et al. (2013) nalezl v explantátech u novorozenců signikantně nižší hladinu tkáňových inhibitorů TIMP-1, než ve tkáních odebraných při zákroku mezi 2. a 4. měsícem věku. Vyšší obsah tohoto proteinu v dospělé tkáni souvisí s tvorbou jizev. Tento výsledek je slibným poznatkem k dalšímu studiu hojení jizev v souvislosti s načasováním operace. Mcheik et al. popisují excelentní estetickou kvalitu provedené operace rtu a nosu. Hodnocení pacientů probíhá na základě fotografií, z nichž je posuzována potřeba revizního zákroku. Pacienti jsou operováni během prvního měsíce života v průměru 13. den klasickou metodou dle Millarda. Co se týče potřeby revize, nenacházejí autoři významný rozdíl v porovnání s PCH, nicméně u donošených novorozenců jednoznačně podporují časnou operativu (Mcheik et al., 2006). Hodnocení atraktivity v souvislosti s různým načasováním operace nepřináší z pohledu týmu Goodacre et al. (2004) žádné významné přednosti ve prospěch NCH oproti pozdní operativě. Studie hodnotí NCH pacienty ze dvou různých center a neuvádí operační protokol. V souvislosti s výsledky se domnívají, že důležité pro volbu mezi NCH a PCH budou zejména psychologické následky jednotlivých protoklů na rodinu dítěte. Borský hodnotí estetický výsledek časné operace s odstupem minimálně jednoho roku, na základě posouzení vzhledu pacientů plastickými chirurgy a laickými posuzovateli. Shoda mezi posuzovateli byla testována zvlášť pro jednotlivé skupiny, i pro všechny dohromady Krippendorffovým indexem alfa pro pořadová data. Lepší vzhled jizvy u dětí operovaných v neonatálním období je hodnocen jako statisticky významný. Pacienti byli operování modifikovanou

metodou dle Tennisona či Veau (dle typu vady) mezi 1. a 8. dnem po narození (Borsky, 2014).

V rámci našeho projektu hodnotíme pacienty, kteří jsou operováni jedním operatérem (MUDr. Jiří Borský, PhD.) modifikovanou metodou dle Tennisona u jednostranných vad a metodou podle Veau modifikovanou pro oboustranné rozštěpy. Modifikace pro jednostranné vady spočívá v doplnění dvěma laloky, které jsou získané sklopením okrajů rozštěpové štěrbiny. Jeden z laloků slouží k prohloubení vestibula a spodiny dutiny nosní, druhý lalok pak umožňuje prohloubení a doplnění horního vestibula ústního. Laloky poskytují materiál navíc a umožňují snadnější modelaci rtu a nosu, obzvláště u závažnějších vad (Obr 1.A). Modifikace dle Veau spočívá ve zvednutí dvou slizničních laloků na mezičelisti, které jsou použity k prohloubení horního ústního vestibula a dále dvou slizničních laloků k prohloubení vestibula a spodiny nosní. Tato modifikace umožňuje snadnější modelaci rtu a nosu bez současného napětí modelovaných tkání (Obr 1.B). Detailní popis metody v Borsky et al. 2012 a Borský 2014.



Obr 1. Schéma operačního postupu: A) dle Tennisona modifikovaného pro jednostranný rozštěp rtu; B) dle Veau modifikovaný pro oboustranný rozštěp rtu.
1- stav těsně před operací; 2 a 3- preparace: VL-slizniční lalůček/ky k prohloubení vestibula, NL-slizniční lalůček/ky k prohloubení boku a spodiny nosní; 4- stav po operaci (převzato a upraveno dle (Borský, 2014).

Palatoplastika

Druhá operace, kterou pacienti s kompletní rozštěpovou vadou podstupují, je rekonstrukce patra. Palatoplastika během let doznala také značného vývoje, zejména co se načasování týče, nicméně vliv operace patra na růst obličeje není cílem této práce, proto detailnější popis nebyl do disertace zařazen. Dle řady studií navíc nemá palatoplastika na vývoj obličeje zdaleka tak zásadní vliv, jako cheiloplastika (Hagerty and Hill, 1963; Kremenak, 1967; Bardach and Eisbach, 1977; Eisbach et al., 1978; Bardach, 1990; Capelozza et al., 1996). Ross (1987) nepozoruje podstatné rozdíly v růstu horní čelisti u pater operovaných různými technikami během prvních deseti let života, přestože v palatoplastice vidí příčinu redukce růstu maxily. Ve studii zabývající se vlivem sekundární spongioplastiky (Caganova et al., 2014), byla patra všech pacientů operována v průměru ve 4 letech metodou dvou laloků, retropozice a faryngofixace (Kuderova et al., 1996). Studie, zabývající se vlivem neonatální cheiloplastiky (Dadáková et al., 2016; Moslerová et al., 2018), hodnotí soubor pacientů, kteří podstoupili palatoplastiku metodou dle Furlowa v průměrném věku 10 měsíců (Borsky, 2014).

Sekundární spongioplastika

Hledání ideálního řešení defektu alveolu trvalo značnou dobu a prošlo do současnosti řadou významných změn. Primární osteoplastika (PO) neboli primární štěpování, které se provádělo souběžně se suturou rtu nebo později, zpravidla ve věku mezi 1. a 3. rokem, mělo za cíl nahradit chybějící kost a tak zabránit pooperační kompresi a kolapsu maxily (Dušková et al., 2007). Představa, že časná osteoplastika přemění defektní tkáň ve víceméně zdravou čelist, se bohužel nenaplnila, a výsledkem byla dlouhodobá inhibice růstu maxily z důvodu příliš časného zásahu do růstových zón (Bergland et al., 1986a; Dušková et al., 2007). Důsledkem významně narušeného maxilárního růstu je pseudoprognacie a zkřížený skus, jež se zvýrazňují s věkem. U dospělých jedinců je popisován výrazně konkávní profil. Štěp během vývoje pacienta neroste a zuby jím spontánně neprořezávají. Po provedených studiích autoři doporučovali od metody upustit (Pickrell et al., 1968; Friedel and Johanson, 1974; Robertson and Jolleys, 1983). Primární periosteoplastika (PP), která měla nahradit PO, spočívá v přemostění rozštěpu elastickým periostálním lalůčkem. Lalůček propojuje poškozenou čelist nejdříve elasticky, později osifikuje v kostěnou lamelu, čímž se mělo

lépe a rychleji docílit vyrovnání předního intermaxilárního segmentu a segmentů laterálních, než tomu bylo v případě primární osteoplastiky (Kuderova et al., 1996). Periosteoplastika se prováděla nejčastěji společně s cheiloplastikou, ale zákrok býval posunut i do vyššího věku (2–10 let) (Kuijpers-Jagtman and Long, 2000). Autoři uvádějí lepší výsledky v porovnání s PO (Hellquist and Skoog, 1976; Šmahel and Mullerová, 1988), ale ani tato metoda celkově nenaplnila očekávání odborníků (Bergland et al., 1986b; Amanat and Langdon, 1991). Poněkud lepší výsledky přinesla metoda opožděné PP, kdy autoři uvádějí osifikaci v 80% případů (Hellquist et al., 1983). Jabbari et al. (2017) nepopisuje signifikantní rozdíl v délce maxily u pacientů s PP a SS v 18 letech, nicméně přechodný signifikantní rozdíl byl sledován v nižším věku (5 a 10 let). Přestože se zdá, že PP z dlouhodobého hlediska výrazně neredukuje růst horní čelisti (Jabbari et al., 2017), její efekt ve smyslu rekonstrukce alveolárního hřebene je mizivý a velká část pacientů musí v pozdějším věku podstoupit SS (Matic and Power, 2008; Jabbari et al., 2017).

Vzhledem k neuspokojivým výsledkům výše uvedených technik, byla k překonání obtíží spojených s postižením alveolu zavedena metoda sekundárního štěpování, tzv. sekundární spongioplastika (Amanat and Langdon, 1991). Sekundární spongioplastika (SS) byla poprvé představena autory Boyne & Sands (1972) a výrazně propagována kolektivem dr. Abyholma (Abyholm et al, 1981 cit. podle Amanat & Langdon 1991). V současné době je SS považována za spolehlivou standardně využívanou metodu k řešení defektu alveolu, jejíž finální výsledky jsou velice dobře předvídatelné, (Kawakami et al., 2004; Feichtinger et al., 2008). Podstatou SS je stabilizovat maxilární segmenty a obnovit integritu alveolárního hřebene, usnadnit finální protetické zákroky zlepšením vztahu vestibulárních měkkých tkání, uzavřít oronazální píštěle, předejít obstrukcím dýchacích cest a zejména pak umožnit erupci zubů místem rozštěpového defektu spolu s umožněním pohybu zubům sousedícím s okrajem defektu tak, aby bylo dosaženo správné polohy v rámci zubního oblouku bez potřeby protetických náhrad. Dalším benefitem je zisk skeletální podpory nosní baze a rtu a tím dosažení vyšší symetrie oronazální oblasti (Amanat & Langdon 1991; Bergland et al. 1986; Devlin et al. 2007; Kawakami et al. 2003; Kawakami et al. 2004; Semb 1988). Samotný zákrok spočívá ve vyplnění defektu horní čelisti drobnými spongiózními štěpy, které jsou nejčastěji odebírány z lopaty kosti kyčelní (Bergland et al., 1986a; Coots, 2012), odkud se dá snadno odebrat velké množství spongiózní kosti (Bergland et al., 1986a). SS se provádí v období výměny dentice mezi 6 - 12 rokem,

nejčastěji pak mezi 9 a 11 rokem před prořezáním trvalého špičáku (Witsenburg, 1985; Bergland et al., 1986a; Semb, 1988; Amanat and Langdon, 1991; Newlands, 2000; Dempf et al., 2002; Kawakami et al., 2003; Dušková et al., 2007; Feichtinger et al., 2008). Autoři uvádějí, že pokud se SS provede před erupcí stálého špičáku, je dosaženo lepší stability štěpu oproti případům, kdy je zákrok proveden až po prořezání špičáku (Bergland et al., 1986a; Newlands, 2000; Dempf et al., 2002). Nejsou také pozorovány rozdíly v přijetí štěpu mezi UCLP a BCLP pacienty (Bergland et al., 1986a). Řada studií udává úspěšnost metody SS hodnocené podle "Oslo Grading System" mezi 80-90%. Například Bergland et al. (1986) u zákroku provedeného před erupcí špičáku udává u výšky interdentálního septa dosažení kategorie I v 64% a kategorie II ve 32%. Uzavření štěrbiny je dosaženo asi v 90% případů. Newlands (2000) uvádí spontánní prořezání špičáků v 64 z 94 případů a dosažení kategorie I či II celkově v 91% případů. I další práce udávají podobně vysoké míry úspěšnosti (Abyholm et al., 1981; Dempf et al., 2002)(Dayashankara Rao et al., 2012). Paterson et al. (2016) porovnávají dva soubory jedinců operovaných SS na stejném pracovišti v časovém odstupu několika let (první skupina 2000-04 druhá skupina 2007-10) a popisují výrazné zlepšení na stupnici „Kindelan bone-fill indexu“ u druhé skupiny pacientů. Na základě těchto výsledků potvrzují významný posun pracoviště v úspěšnosti provedení zákroku během let. Feichtinger et al. (2008) jsou více skeptičtí, co se předchozích dosažených výsledků týče. Principem hodnocení na 2D Rtg snímcích je korelace mezi výškou kosti a celkovou hodnotou resorpce, přičemž autoři poukazují na četné limitace metody, jako je zvětšení a zkreslení, překrytí přilehlých struktur, omezený počet identifikovatelných orientačních bodů a obtíže při jejich umístění. Jejich výsledky hodnocením pomocí CT snímků ukazují resorpci kosti v prvním roce po SS na 49% původní kosti, po druhém roce na 48%. Van Der Meij et al. (2001) popisuje 30% úbytek kosti v odstupu jednoho roku u UCLP pacientů, u BCLP jedinců je resorpce kosti ještě daleko vyšší a dosahuje hodnot 55%. Výrazně větší úbytek kosti, než popisovaly konvenční 2D metody, byl nalezen také ve studii (Reddy et al., 2015).

Recentní studie Jabarri et al. (2018) však podstatně zmírňuje předchozí kritiku hodnocení metodou telerentgenografie. Ve své práci autoři hodnotí v 10ti- a 20tiletém odstupu resorbci kostního štěpu u UCLP pacientů a současně s tím, u jedinců po 20 letech pořizují společně s kontrolním Rtg snímkem CBCT snímek (cone beam computed tomography). Prvním zjištěním je fakt, že během druhé dekády dochází k další resorpci přibližně u poloviny pacientů. Pomocí CBCT však autoři nepočítají

objem štěpu, ale hodnotí výšku septa na základě Berglandova skórovacího systému (Bergland et al., 1986a). Prvním důvodem je významné setření hranic mezi štěpem a okolní kostí po 20 letech, druhým absence údajů z CT o objemu štěpu po prvních 10 letech a třetím snaha porovnat obě metody na základě stejného metodologického přístupu. Z jejich studie vychází řada hodnotných závěrů. Výsledky hodnocení na škále podle Berglanda pomocí Rtg a CBCT jsou v naprosté shodě. Autoři naznačují, že hodnocení na základě Rtg snímků je k hodnocení resorpce štěpu vhodné a dostačující a má ve srovnání s CT snímkováním jisté výhody (dostupnost, nižší náklady, nižší dávka záření). Další výsledky ukazují, že pacienti s kompletním rozštěpem jsou více ohroženi periodontitidou, přičemž pacienti léčeni fixními nebo snímatelnými aparátky mají vyšší riziko progrese tohoto onemocnění. Z longitudnálního sledování vyplývá, že zvýšená resorpce štěpu pozitivně souvisí se stavem zánětu (Jabbari et al., 2015, 2018).

Z výše uvedeného souhrnu vyplývá, že posuzování vlivu jednotlivých operačních metod na kraniofaciální vývoj má své hluboké opodstatnění a v rámci zkvalitňování péče o pacienta, ve snaze co nejvíce zmírnit následky vrozené vady, je stále nedoceněné.

2 Cíle práce

Základním tématem výzkumu bylo sledovat obličej pacienta s rozštěpem z různých úhlů pohledu v návaznosti na dva terapeutické přístupy. Hlavními cíli bylo 1) popsat růst patra během prvních deseti měsíců života UCLP pacientů, objasnit, zda má neonatální cheiloplastika během sledovaného období negativní vliv na růst maxily a vyhodnotit, jakým způsobem je růst patra ovlivněn v souvislosti s typem a závažností vady; 2) popsat odchylky v morfologii měkkých tkání a asymetrie obličeje u dětí předškolního věku s různě závažnou rozštěpovou vadou v porovnání s normou, sledovat případné vývojové trendy a získat informace o vlivu NCH na růst a vývoj obličeje; 3) popsat vliv sekundární spongioplastiky na vývoj obličeje u dospívajících chlapců v odstupu 5 let po implantaci štěpu v porovnání s efektem předchozího operačního protokolu zahrnujícího metodu primární periosteoplastiky.

Poslední cíl disertace se týkal tématu zdravých kontrolních jedinců, jež jsou obecně nepostradatelnou součástí klinických studií založených na popisu odchylek patologie od normy. Stanovili jsme si zmapovat kritickou periodu pubertálního období, přičemž dílčími cíli bylo zhodnotit variabilitu tvaru a formy obličeje chlapců a dívek ve věku od 12 do 15 let, identifikovat sexuálně dimorfní znaky a popsat rozdíly mezi jednotlivými věkovými kategoriemi.

3 Souhrn předkládaných publikací

3.1 Vliv neonatální cheiloplastiky na vývoj patra u pacientů s orofaciálními rozštěpy

Efektu NCH na růst horní čelisti v prvních deseti měsících života, mezi cheiloplastikou a palatoplastikou, jsme se věnovali ve dvou studiích (Hoffmannova et al., 2016; Hoffmannova et al., 2018). V tomto období nedochází k ovlivnění žádným jiným chirurgickým zákrokem a růst patra a jeho změny jsou pouze v důsledku kombinace NCH a rozštěpové vady jako takové. Obě práce byly založeny na hodnocení 3D modelů sádrových odlitků patra metodami klasické a geometrické morfometrie. Každému pacientovi byly sejmuty otisky dvakrát, poprvé před NCH a následně v odstupu přibližně 10 měsíců před palatoplastikou. Sádrové odlitky pater byly skenovány pomocí skeneru Breuckmann SmartScan scanner (Aicon 3D Systems GmbH, Braunschweig, Germany). Pro veškeré úpravy modelů byl využíván RapidForm XOS software (INUS Technology Inc., Seoul, South Korea), následné statistické analýzy byly provedeny a výstupy získány za využití softwaru Morphome3cs (cgg.mff.cuni.cz/trac/morpho). Základem bylo přesné nanesení 11 landmarků reprezentujících charakteristické struktury novorozeneckého a kojeneckého patra (modifikováno dle Huang et al. 2002).

V práci **Hoffmannova et al. (2016)** jsme si jako dílčí cíle stanovili: 1) detailně popsat morfologii horní čelisti 33 UCLP jedinců, 2) postihnout změny osmi důležitých parametrů popisujících patro a 3) jejich vývojový trend porovnat s publikovanými daty kontrolních jedinců (K*; Kramer et al., (1994)) a jedinců operovaných pozdní cheiloplastikou v průměrném věku 6 měsíců (PCH*; Mishima et al., (2001)). Předpokládali jsme, že NCH má formativní účinek na dentoalveolární oblouk postižené horní čelisti, ale nelimituje růst jednotlivých segmentů v anteriorním směru. Dalším předpokladem bylo, že výsledný růstový trend parametrů horní čelisti bude u NCH pacientů srovnatelný nebo příznivější než u PCH* jedinců. Během studovaného období došlo u našich NCH pacientů k signifikantním změnám všech měřených rozměrů, s výjimkou vzdálenosti mezi budoucími špičáky (anteriorní dentoalveolární šířky), která zůstala beze změny. Rozměry popisující šířku rozštěpové štěrbiny a úhel s tím související, se následkem sutury rtu během sledovaného období podle očekávání zmenšily. Ostatní parametry týkající se posteriorní části horní čelisti zahrnující šířku

dentoalveolárního oblouku, délku obou molárních segmentů a celkovou délku patra, se naopak signifikantně zvětšily.

Změny ve variabilitě povrchu patra byly hodnoceny metodami geometrické morfometrie, konkrétně PCA analýzou. Variabilita souboru se během sledovaného období zmenšila, z čehož vyplývá, že růst horní čelisti u neonatálně operovaných dětí procházel stejnými změnami a sledoval podobný růstový trend. Za použití CPD-DCA analýzy (Dupej et al. (2014)) jsme modelovali růst obou patrových segmentů. Zjistili jsme, že růst segmentů probíhal na anteriorních i posteriorních koncích, což se shoduje s výsledky Huang et al. (2002), a naznačuje, že časná ani pozdní operativa nelimituje posteriorní růst segmentů horní čelisti. Na rozdíl od našich výsledků dokládá řada prací výrazně redukovaný anteriorní růst u svých souborů (Kramer et al., 1992, 1994; Honda et al., 1995; Braumann et al., 2003) a popisované zmenšení rozštěpové štěrbiny je velmi pravděpodobně v důsledku tlaku operovaného rtu (Akin et al., 1991; Kramer et al., 1994; Mishima et al., 2001; Huang et al., 2002). Naopak u našeho NCH souboru je zúžení rozštěpové štěrbiny způsobeno kombinací modelačního efektu cheiloplastiky současně s růstem lokalizovaným na předních koncích obou segmentů horní čelisti. Vzhledem k tomu, že se nesnižuje parametr anteriorní dentoalveolární šířky, zmenšení rozštěpové štěrbiny není zapříčiněno zúžením oblouku horní čelisti.

Z porovnání našich jedinců s K* a PCH* soubory vyplynuly následující poznatky. Posteriorní šířka dentoalveolárního oblouku mezi tubery a vzdálenost mezi špičáky byla v porovnání s K* nalezena vyšší u obou operačních přístupů (NCH i PCH*) a obecně byla popisována větší v řadě studií u pozdně operovaných jedinců (Huddart et al., 1969; Wada and Miyazaki, 1975; Kramer et al., 1992, 1994; Mello et al., 2013). V porovnání s K* byla přítomna také nižší počáteční délka patra u NCH i PCH*, což ve svých pracích uvádí také Kramer et al. (1994) a Kramer et al. (1996). Sakoda et al. (2017) uvádí zkrácení přední délky patra (vzdálenost linie přední šířky oblouku a bodu I-landmark mezi budoucími řezáky) u UCLP jedinců mezi cheiloplastikou a palatoplastikou, jako důsledku modelačního efektu sutury rtu v souvislosti se sklopením nepostiženého segmentu směrem k postiženému. Celková délka patra nicméně v tomto období narůstá. V čase palatoplastiky je přední i celková délka patra UCLP jedinců srovnatelná s hodnotami u pacientů s izolovaným rozštěpem patra. Oba tyto parametry v následujícím roce po palatoplastice narůstají a ve dvou letech věku nejsou mezi UCLP a CP výrazné rozdíly. Růst patra do délky má tedy u obou typů vady stejný trend a nezdá se být ovlivněn suturou rtu. Parametr posteriorní šířky

dentoalveolárního oblouku se u našeho NCH souboru s časem signifikantně zvětšuje, což je obecně popisováno u PCH souborů i zdravých jedinců (Wada and Miyazaki, 1975; Kramer et al., 1992, 1994; Honda et al., 1995; Huang et al., 2002; Sakoda et al., 2017), nicméně v námi porovnávaném PCH* souboru tento parametr v období po cheiloplastice klesá. Jedním z nejvýznamnějších zjištění je informace o rozměru anteriorní dentoalveolární šířky, jejíž hodnota zůstává během sledovaného období nezměněna. Dle dostupné literatury dochází k nárůstu tohoto parametru pouze u zdravých jedinců (Kramer et al. 1994), přičemž Wada & Miyazaki (1975) popisují dokonce nesignifikantní snížení tohoto rozměru. Stejně jako u námi porovnávaného souboru PCH* je u PCH jedinců v období následujícím po sutuře rtu uváděno signifikantní snížení anteriorní dentoalveolární šířky (Huddart et al., 1969; Wada and Miyazaki, 1975; Kramer et al., 1994; Honda et al., 1995; Huang et al., 2002; Braumann et al., 2003; Sakoda et al., 2017). Toto růstové selhání je patrné i u souboru Sakoda et al. (2017) a naznačuje, že operace rtu ovlivňuje zejména anteriorní dentoalveolární šířku, nikoli celkovou délku patra. Anteriorní dentoalveolární šířka je tedy zásadním parametrem určujícím úspěšnost operativy. Vzhledem k tomu, že u našich jedinců ke snížení tohoto parametru nedochází, růstový trend anteriorní dentoalveolární šířky má charakter blížící se normě.

V navazující studii **Hoffmannova et al. (2018)** jsme si stanovili za cíl: 1) popsat jakým způsobem typ a závažnost rozštěpové vady ovlivňují růst horní čelisti, 2) porovnat růstové trendy našich pacientů s publikovanými daty kontrol (K*) a PCH* souboru, převzatých z práce Kramer et al. (1994). Tato studie byla založena na hodnocení dvou typů rozštěpu: kompletního jednostranného rozštěpu rtu, čelisti a patra (cUCLP; n=36) a jednostranného rozštěpu rtu, čelisti a patra s mostem (UCLP+b; n=20). Předpokládali jsme, že s velikostí vady bude narůstat vliv cheiloplastiky na utváření dentoalveolárního oblouku. Dalším předpokladem bylo, že růst horní čelisti jedinců s mostem bude méně zasažen. Pomocí PCA analýzy jsme porovnali variabilitu souborů, přičemž variabilita závažněji postižených jedinců cUCLP souboru byla po narození výrazně větší, než variabilita UCLP+b. Tento rozdíl nejvíce vysvětluje PC1, která je zodpovědná zejména za závažnost rozštěpové vady (velikost rozštěpu). Během prvních deseti měsíců života variabilita cUCLP významně klesla a v období před palatoplastikou se významně překrývala a byla srovnatelná s variabilitou UCLP+b. Pomocí dvoufaktorové ANOVy jsme také hodnotili vliv typu vady, její závažnosti (mírná, střední, těžká) a jejich vzájemné interakce na růst horní čelisti během prvního

roku života. Zjistili jsme, že obě charakteristiky i jejich interakce měly vliv na míru redukce rozštěpové štěrbiny a anteriorního bazálního úhlu, stejně tak jako na nárůst posteriorní šířky dentoalveolárního oblouku. Tato zjištění byla v souladu s výsledky Kramer et al. (1992). Typ i závažnost vady také ovlivňují anteriorní šířku dentoalveolárního oblouku, na ostatní hodnocené parametry vliv nemají. U našeho souboru nebyla nalezena signifikantní korelace mezi velikostí defektu a délkou patra. To je velmi důležitý poznatek, protože právě negativní efekt závažnosti vady byl v řadě studií uváděn jako jeden z faktorů hrajících roli při redukci růstu horní čelisti (Mazaheri et al., 1993; Peltomäki et al., 2001; Liao et al., 2010). Pokud jsme porovnali cUCLP a UCLP+b ve smyslu změny parametrů ve sledovaném období, signifikantní rozdíly se manifestovaly v anteriorních oblastech segmentů, jako je šířka defektu a anteriorní bazální úhel. Ty výrazněji klesaly u cUCLP. Naopak větší nárůst posteriorní šířky oblouku byl pozorován u UCLP+b, což je v souladu s výsledky uvedenými výše. Růstové trendy anteriorní a posteriorní šířky dentoalveolárního oblouku a délky patra byly porovnány s růstovými trendy PCH* a K*. Z výsledků tohoto deskriptivního porovnání vyplynulo, že růstové trendy u parametrů posteriorní šířky oblouku a celkové délky patra u jednotlivých typů vady vykazovaly výraznou podobnost s růstovými trendy 2 sledovaných skupin PCH* a obecně také s K* (Kramer et al., 1994). Parametrem, u kterého se růstové trendy lišily, byla anteriorní šířka oblouku. Ta u našich pacientů zůstala beze změny (cUCLP) nebo se s věkem zvýšila (UCLP+b). Zvýšení tohoto parametru bylo popsáno také u K*, zatímco u PCH* došlo k jeho snížení. Tyto poznatky pomohly doplnit celkový obraz o růstu horní čelisti z předchozí studie. Zároveň byla potvrzena absence zúžení přední dentoalveolární šířky následkem NCH u obou typů vady. Možným vysvětlením může být odlišná technika řešení defektu rtu modifikovaná dle původní metody podle Tennisona. Modifikace přináší více materiálu do oblasti sutury a snižuje tak tlak rtu po zákroku (Borsky et al., 2012). U PCH pacientů byla popsána redukce tohoto parametru, což nasvědčuje výrazně vyššímu laterálnímu tlaku na maxilární segmenty (Wada and Miyazaki, 1975; Kramer et al., 1994; Honda et al., 1995; Huang et al., 2002; Sakoda et al., 2017). Z výsledků 3D modelování růstu vyplynulo, že v anteriorních oblastech probíhal růst u obou skupin shodně. Posteriorní části obou segmentů rostly poněkud výrazněji u UCLP+b v porovnání s cUCLP jedinci. Růst v anteriorních oblastech byl potvrzen také přímou 2D morfometrií, společně s uzavíráním rozštěpové štěrbiny a zmenšováním anteriorního bazálního úhlu. Celkově můžeme shrnout, že neonatální cheiloplastika v případě

kompletních i nekompletních jednostranných vad neměla v prvním roce života reduktivní efekt na růst horní čelisti. Byl zde přítomen modelační efekt na alveolární oblouk a vzájemné přiblížení anteriorních okrajů obou segmentů, aniž by se předčasně setkaly či navzájem překřížily. Tento efekt byl více patrný u závažnějšího postižení (cUCLP). Navíc nebylo nalezeno zúžení v anteriorní oblasti dentoalveolárního oblouku, což je klasický nález u UCLP pacientů po operaci rtu. U pacientů s mostem se tento parametr naopak zvyšuje. Oba segmenty rostly v anteriorních i posteriorních oblastech, nebylo nalezeno zkrácení délky patra následkem NCH a růst horní čelisti celkově vykazoval trendy podobné K*.

3.2 Vliv neonatální cheiloplastiky na vývoj obličeje a rozvoj asymetrie u pacientů s orofaciálními rozštěpy

V rámci této části našeho projektu jsme se ve studiích Dadáková et al. (2016) a Moslerová et al. (2018) soustředili na sledování vývoje obličeje a manifestaci obličejové asymetrie předškolních dětí operovaných neonatální cheiloplastikou. Podkladem studií byly 3D modely obličeje dětí dvou věkových kategorií (3 a 4,5 roku) s různě závažným typem rozštěpové vady (UCL, UCLP, BCLP) a kontrolní soubor sestávající ze zdravých jedinců (žáci mateřských škol). Data byla hodnocena pokročilými metodami geometrické morfometrie. Obličejové skeny byly pořízeny faciálními skenery Vectra 3D (Canfield Scientific Inc., Fairfield, NJ, USA) a 3dMDface System (3dMD Limited, Brentford, London, UK). Veškeré statistické zpracování a analýzy byly provedeny za pomoci softwaru Morphome3cs. Výsledné tvarové odchylky a přítomná asymetrie byly vizualizovány pomocí barevných map a map signifikance.

Cílem studie **Dadáková et al. (2016)** bylo posoudit vývoj hlavních odchylek morfologie obličeje u souboru 72 pacientů předškolního věku v porovnání s věkově odpovídající normou (n=60) a popsat případný vývojový trend těchto abnormit. Úvodní statistické testování Hottelingovým T2 testem na PC skóre našich jedinců potvrdilo, že mezi věkovými kategoriemi nejsou v celkovém průměrném tvaru obličeje v rámci jednotlivých typů vady signifikantní rozdíly. Nicméně pro detailní zachycení případných drobných změn během růstu byly vizualizovány obě věkové kategorie. Všechny sledované skupiny orofaciálních rozštěpů se signifikantně lišily od normy, dokonce i v případě nejméně závažné vady (UCL). Signifikantní rozdíly morfologie

obličeje mezi věkovými kategoriemi, které jsme zachytili na základě barevných map, se vyskytují zejména v oblasti čela (kontroly, UCL, BCLP), v odlehlých laterálních oblastech tváří (UCL) a nevýznamně v oblasti brady (UCLP, BCLP). V oblastech přímo se vztahujících k rozštěpové vadě, jako je nos, filtrum či oblast retní červeně, se signifikantní změny neodehrály. Celkově odpovídaly nalezené hlavní odchylky v morfologii obličeje standardně popisovaným odchylkám rozštěpových pacientů (Smahel and Brejcha, 1983; Capelozza et al., 1996; Ferrario et al., 2003). U obou skupin CLP pacientů (jedno/oboustranný rozštěp rtu, čelisti a patra) bylo patrné mírně ubíhající čelo. Redukční efekt chirurgických intervencí u CLP pacientů, manifestovaný mimo oblast samotných zákroků až do oblasti čela, popisuje ve své práci Duffy et al. (2000). Ubíhající frontální oblast byla nalezena také u pacientů ve studii Djordjevic et al. (2014). Nosní kořen byl oproti normě u UCL a UCLP jedinců méně konkávní, což se lehce zdůraznilo s věkem. Nosní hrot u UCLP souboru byl pouze v lehké retruzi. U BCLP jedinců byl hřbet nosu širší a od kořene výrazněji oploštělý, odchylka byla významná v obou věkových kategoriích a v porovnání s jednostrannými vadami se zde manifestovala mnohem výrazněji. Nižší konkavita nosního kořene společně s dalšími odchylkami obecně přispívá k typickému oploštění profilu rozštěpových pacientů. Míra oploštění obličeje pak závisí na vzájemné kombinaci tvaru nosu, retruze maxily a protruze mandibuly (Capelozza et al., 1996; Ferrario et al., 2003). U UCL jedinců jsme detekovali poněkud širší a plošší nosní křídlo postižené strany. Tato odchylka byla nalezena i u UCLP pacientů. BCLP jedinci vykazovali rozšíření a oploštění nosních křídel bilaterálně, což je v souladu s nálezy studie Bugaighis et al. (2014b). Deformity nosu jsou obecně považovány za zásadní problém terapeutické a estetické léčby pacientů s rozštěpem (Duffy et al., 2000; Ayoub et al., 2003; Bugaighis et al., 2010, 2014c). Deviace kolumely směrem k nepostižené straně v důsledku přerušení *m. orbicularis oris* a nemožnost obnovit absenci mediálních úponů obličejových svalů během primárních operací zřejmě přispívá k rozvoji výše popisovaných odchylek (Zreaqat et al., 2012). U UCL jedinců byla patrná prominence tkáně v oblasti pooperační jizvy. U UCLP jedinců byla oblast jizvy na stejné úrovni jako u kontrol, což bylo způsobeno retruzí okolní tkáně, která zasahuje i laterálně oblast tváří a svědčí pro zkrácení horní čelisti. Maxilární retruzi popsali u PCH jedinců také Bugaighis et al. (2010) a Djordjevic et al. (2014). Oblast premaxily BCLP jedinců byla společně s dolním rtem ve výrazné protruzi. Nicméně stejně jako u UCLP jedinců byla patrná retruze v oblasti tváří popsaná ve studii Duffy et al. (2000). Tato odchylka se lehce

zvýrazňovala s věkem. Oblast maxily je obecně u pacientů s rozštěpem považována za vůbec nejproblematičtější. U BCLP jedinců jsou odchylky v této oblasti z důvodu vrozeného předsunutí premaxily vyjádřeny závažněji než u jednostranných vad (Honda et al., 1995; Capelozza et al., 1996; Diah et al., 2007). Menší konvexita byla nalezena také u kontury měkkého profilu dolní čelisti UCL jedinců. Tato odchylka byla výraznější v mladším věku. Naopak celkově prominující brada byla popsána u starších UCLP a BCLP jedinců, což zapadá do celkového obrazu vývoje dolní čelisti u CLP pacientů (Smahel and Brejcha, 1983). Nejméně postižení a normě nejvíce podobní jedinci byli ve skupině UCL pacientů. Naopak nejvýrazněji se odchylky od normy manifestovaly u nejtěžšího postižení, tedy u BCLP jedinců. U UCL jedinců byla jedinou odchylkou maxilární oblasti prominence v místě jizvy, retruze laterálních partií zde nebyla přítomna. Toto zjištění naznačuje, že na růst zdravé maxily nemá časná sutura rtu během sledovaného období inhibiční vliv. Odchylky morfologie obličeje u jednotlivých skupin jsou v rámci typických odchylek rozštěpových pacientů, přičemž v předškolním období nenacházíme jejich signifikantní progresi s věkem. Vzhledem k výše uvedeným závěrům a celkovému vývoji obličeje pacientů se NCH zdá jako adekvátní metoda chirurgického řešení rozštěpu rtu.

Práce **Moslerová et al. (2018)** měla v rámci studia obličeje rozštěpových pacientů za cíl zhodnotit přítomnost asymetrie a posoudit, zda je s věkem patrná její progrese. Hodnocení asymetrie kontrolního souboru pak mělo detekovat výskyt možných paralel s rozštěpovými skupinami. Materiálem byl rozšířený soubor předchozích jedinců (96 pacientů s rozštěpem; 78 zdravých kontrol). Hottelingovým testem jsme vyloučili signifikantní rozdíly mezi věkovými kategoriemi. Významně se však všechny skupiny rozštěpů svou asymetrií lišily od normy. Oproti hodnocení tvarových odchylek, byli z pohledu asymetrie více postiženi jedinci s jednostrannou vadou, než jedinci postižení oboustranně. Tento poznatek je ve shodě s výsledky práce Bugaighis et al. (2010) a Bugaighis et al. (2014a) a naznačuje, že zde neplatí pozitivní korelace mezi závažností vady a mírou asymetrie. Jednostranný charakter vady má oproti oboustranným vadám vyšší vliv na rozvoj asymetrie. Pro detailní vizualizaci odchylek od symetrie v jednotlivých oblastech obličeje jsme opět využili barevných map. U všech skupin pacientů jsme nalezli asymetrii čela, která patrně nesouvisela s rozštěpovou vadou. Základem tohoto předpokladu byla přítomnost pozitivních odchylek od perfektní symetrie shodně na pravé straně u pravo- i levostranných rozštěpů a současně také u normy. Asymetrie čela vznikla nejspíše jako následek posturální plagiocefalie

v kojeneckém věku, která vede k protruzi čela na straně okcipitálního oploštění (Slovis et al., 2013). Incidence plagiocefalie dosahuje až k 50% (Mawji et al., 2013), s vyšší prevalencí na pravé straně (Bridges et al., 2002; Mawji et al., 2013). Nejvyšší stupeň asymetrie byl nalezen v oblasti horního obličeje. U UCL jedinců byla asymetrie vyjádřena zejména v nasolabiální oblasti, s pozitivními odchylkami od symetrie v oblasti filtra a červeně horního rtu, jako důsledek samotné vady a protruze jizvy. Přilehlé nosní křídlo vykazovalo asymetrii v negativních hodnotách. U UCLP jedinců bylo nalezeno totožné schéma asymetrie nasolabiální oblasti jako u UCL jedinců, navíc jsme však detekovali signifikantní asymetrii zasahující laterálně do bukální oblasti, která se mírně zvýrazňovala s věkem. Asymetrie nosu u jednostranných vad vzniká v důsledku kombinace asymetrie skeletálního podkladu a diastázy souvisejících svalů (Fisher and Sommerlad, 2011). Deviace septa v důsledku tahu *m.orbicularis oris* (Latham, 1969) a dysplastická laterální nazální chrupavka (Byrd et al., 2007) vedou k asymetrii nosního hrotu a méně prominující nostrile s širším nosním vchodem na postižené straně. U oboustranných vad byla asymetrie zjištěna v laterálních partiích hřbetu nosu a nosních křídel, s pozitivními hodnotami vlevo, která odtud pokračovala inferiorně do oblasti filtra a přilehlých partií. U starší věkové kategorie zasahovala asymetrie ještě více laterálně do oblasti tváří. Přestože by mělo septum v případě oboustranného postižení zůstat v mediální rovině, méně postižená strana vyvíjí větší tlak na kaudální septum a odchyluje ho k této straně (Kaufman et al., 2012). Oproti jednostranným vadám vykazovali BCLP jedinci pouze mírnou asymetrii nosu. Asymetrie filtra a retní červeně je u rozštěpových pacientů další častou deformitou. Přestože je uváděn velmi uspokojivý vzhled nasolabiální oblasti u pacientů operovaných NCH (Mcheik and Levard, 2006; Mcheik et al., 2006; Borský et al., 2007; Borsky et al., 2012), pooperační hypertrofie jizvy je typickou komplikací rozštěpu rtu (Soltani et al., 2012). Borsky et al. (2012) ve své práci uvádí, že symetrie kontury horního rtu bylo u souboru NCH pacientů dosaženo v 68 %. Hodnocení symetrie v předozadním směru 3D metodami nicméně potvrdilo přítomnost asymetrie u všech skupin pacientů. Přesto, že se jedná o oboustranný defekt, shodně s jednostrannými vadami byla i u BCLP jedinců nalezena mírná asymetrie retní červeně. Stejně jako Russell et al. (2014) se k přikláníme k názoru, že je potřeba přehodnotit předchozí předpoklady, že je ret u bilaterálních vad po cheiloplastice relativně symetrický. Nicméně oproti výše zmiňované studii nacházíme odchylky od symetrie nesignifikantní. Podstatný vliv zde může mít použitá operační metoda. Asymetrie laterálních oblastí

u CLP jedinců souvisí s narušením celistvosti patra. Výsledky práce Al-Rudainy et al., (2018) u UCLP jedinců popisují asymetrii v laterálních oblastech maxily v předoperačním období ve věku 3,5 měsíce, s negativními hodnotami na postižené straně, což je v souladu s našimi výsledky. Je tedy zřejmé, že asymetrie maxily je u kompletních vad odchylkou kongenitální, vyskytující se nezávisle na cheiloplastice či následné palatoplastice. Samotný tvar patra UCLP a BCLP jedinců byl hodnocen v řadě studií pooperačně a jejich výsledky kromě jiných závěrů potvrzují fakt, že se patra u rozštěpových pacientů vyvíjejí asymetricky (Kilpeläinen and Laine-Alava, 1996; Smahel et al., 2004; Šmahel et al., 2009; Bejdová et al., 2012; Rusková et al., 2014). Maximální výška klenby patra UCLP jedinců byla nalezena v posteriorní části nepostižené strany (Smahel et al., 2004; Rusková et al., 2014) a podporuje tak naši teorii, že pozitivní odchylky od perfektní symetrie na nerozštěpové straně souvisejí primárně s odchylkami skeletu. U BCLP jedinců pak Šmahel et al. (2009) popisuje oproti kontrolám větší výšku klenby patra v anteriorní oblasti a naopak nižší výšku v posteriorní oblasti. Ve srovnání s kontrolami je asymetrie patra přítomná a posteriorně se snižuje společně s tím, jak se zmenšuje výška klenby. Toto zjištění je v souladu s našimi výsledky, kdy se u BCLP jedinců ve starším věku asymetrie rozšiřovala do oblasti tváří a laterálně vyznívala. Otázku laterality bude potřeba dále studovat na větším souboru pacientů. V souvislosti s oblastí dolního obličeje byla nalezena různá míra asymetrie dolního rtu, nejvýraznější u UCL jedinců, nejméně manifestovaná u BCLP souboru. Vysvětlením může být nesprávné postavení předních zubů, skeletální deformity mandibuly (Bhuvaneswaran, 2010) či předchozí snaha dítěte dosáhnout bilabiálního uzavření úst s postiženým horním rtem (Pensler and Mulliken, 1988). V oblasti brady byla nalezena pozitivní odchylka od symetrie na straně rozštěpu, což popisují i další autoři (Kim et al., 2013; Kuijpers et al., 2015; Lin et al., 2015). U UCL jedinců našeho souboru byla asymetrie nepatrná a BCLP jedinci vykazovali asymetrii v oblasti brady nekonzistentní v rámci věkových kategorií. U BCLP jedinců byla v literatuře na základě skeletu popsána asymetrie bez rozdílů oproti normě (Kurt et al., 2010; Paknahad et al., 2016). Nejednotnost asymetrie našich BCLP skupin nejsme z důvodu nedostatečnosti dosavadních studií schopni uspokojivě vysvětlit, a vliv může mít také menší počet jedinců. Obecně můžeme shrnout, že nejvýznamnější asymetrie byla nalezena v oblasti samotné rozštěpové vady. U kompletních rozštěpových vad zasahovala i dále laterálně do oblasti maxily, přičemž původ této asymetrie dáváme primárně do souvislosti s narušenou horní čelistí, nikoli chirurgickou léčbou. Izolovaný

rozštěp rtu v kombinaci s časnou operací nevyvinul významnou asymetrii oblastí obličeje přímo nesouvisejících s místem defektu. Pacienti s oboustrannými vadami vykazovali nižší míru a odlišný typ asymetrie od jednostranných vad a jejím celkovým charakterem, vyjma nasolabiální oblasti, se blížili spíše normě. Kromě mírné progrese asymetrie v oblasti maxily u CLP jedinců, se asymetrie v ostatních oblastech s věkem nezvýraznila.

3.3 Vliv SS na vývoj obličeje u pacientů s jednostrannými orofaciálními rozštěpy

Ve studii **Caganova et al. (2014)** jsme se soustředili na rekonstrukci defektu alveolu. Navazovali jsme na sérii prací, které vznikly na základě dat pacientů pracoviště Plastické chirurgie Fakultní nemocnice Královské Vinohrady v minulosti a které se zabývaly vlivem jednotlivých operačních technik úpravy alveolu na kraniofaciální vývoj (Šmahel and Mullerová, 1988; Smahel and Mullerova, 1994; Sameshima et al., 1996; Smahel et al., 1998; Veleminska, 2000). Většina publikovaných prací, týkajících se hodnocení SS, popřípadě jejího porovnání s PP, se soustředila především na stabilitu štěpu ve smyslu úbytku kostní hmoty v odstupu času, či erupci špičáků (Long et al., 1995; Honma et al., 1999; Kawakami et al., 2003; Matsui et al., 2005; Jia et al., 2006; Feichtinger et al., 2007; Matic and Power, 2008; Dayashankara Rao et al., 2012). My jsme si stanovili odlišný cíl: 1) porovnat poslední dvě uvedené metody rekonstrukce alveolu z pohledu dlouhodobého dopadu na růst jednotlivých obličejových struktur, jejich vzájemného postavení a také dopadu na vývoj mezičelistních vztahů v kritické periodě pubertálního růstového období. 2) zjistit, zda nová technika přináší pro pacienty benefity, a pokud ano, tak jaké. Předpokládali jsme, že finální morfologie obličeje pacientů operovaných SS bude vykazovat nižší míru dentálních a skeletálních odchylek než soubor PP pacientů. Sledovaný soubor tvořily laterální telerentgenové snímky (teleRtg) 18 chlapců, kteří v průměrném věku 10,3 roku podstoupili chirurgické řešení defektu alveolu implantací spongiózních štěpů (SS). Srovnávacím souborem byla data 48 chlapců, u nichž byl rozštěp čelisti řešen současně se suturou rtu přemostěním pomocí elastického periostálního lalůčku (PP) v průměrném věku 9 měsíců. Pacienti obou sledovaných souborů podstoupily cheiloplastiku (11m.-SS; 9m-PP) i palatoplastiku zahrnující metodu retropozice s faryngofixací (4r7m-SS; 5r2m-PP) v přibližně stejném věku. Porovnání vlivu obou operačních metod bylo založeno na

hodnocení laterálních teleRtg snímků obličeje pořízených u obou skupin ve věku 10 a 15 let. Nanesení landmarků bylo provedeno v softwaru na analýzu obrazu SigmaScan Pro, výpočet 86 navolených lineárních, úhlových a speciálních mezičelistních rozměrů byl proveden prostřednictvím softwaru Craniometrics (Velemínská et al., 2003). Finální faciogramy byly zkonstruovány v programu AutoCAD 2008 (Autodesk Inc., USA). Abychom mohli jednoznačně popsat vliv obou metod na růst obličeje ve sledovaném pětiletém období, bylo třeba zjistit, zda se skupiny pacientů nelišily již ve věku 10 let. Nalezené rozdíly se týkaly zejména přední výšky horního obličeje a s tím spojené celkové výšky obličeje, která byla nižší u PP pacientů. Důsledkem nižší výšky horního obličeje byla celková vertikální disproporce obličeje u PP pacientů. Nižší výška horního obličeje je jednou z charakteristických odchylek skeletálního růstu, za jejíž původ je považována absence růstových impulzů nazálního septa na kompletně oddělenou stranu postiženou rozštěpem (Smahel and Brejcha, 1983). Vzhledem k výrazně kratší výšce horního obličeje PP pacientů můžeme usuzovat, že PP tento negativní vliv ještě podporuje. Signifikantní rozdíl ve prospěch SS pacientů byl nalezen také u hloubky nosu na měkkém profilu. V 15 letech přetrvával a spíše se lehce zmírňoval rozdíl vertikálních parametrů předního obličeje. Signifikantní rozdíl byl nalezen v nárůstu dentoalveolární výšky maxily, který byl výraznější u SS pacientů. Podobné výsledky byly publikovány v práci Brattstroma (1991), který nachází vyšší dentoalveolární výšku u SS pacientů, ovšem v porovnání s jedinci operovanými primární osteoplastikou (PO), nikoliv PP. Rozdíly v celkové délce maxily jsme neprokázaly, což je popisováno i v recentní práci Jabbari et al. (2017), která nám zpětně umožňuje porovnat naše výsledky s totožným metodologickým přístupem. Shodujeme se i v hodnocení pozice horní čelisti, která se během sledovaného období dostala do mírné retruze (Jabbari et al., 2017), přičemž celkový nárůst maxily do délky byl u obou skupin našich pacientů (SS i PP) jen velmi malý. Významné rozdíly nebyly nalezeny ani v souvislosti s mandibulou. Mírná anteriorotace a nesignifikantní protruze dolní čelisti, zapříčiněná výraznějším růstem těla mandibuly v průběhu pubertálního spurtu oproti bazi lební, se vyskytovala shodně u obou skupin a je v souladu se zjištěními Jabbari et al. (2017). Projevem retruze redukované maxily společně s mírnou protruzí mandibuly bylo nesignifikantní oploštění skeletálního profilu. Konvexita skeletálního profilu klesla u obou skupin pacientů téměř rovnoměrně. Tento trend je u rozštěpových pacientů obecně popisován (Šmahel and Brejcha, 1985; Ross, 1987b; Veleminska, 2000). Významný rozdíl jsme nalezli u parametrů popisujících sklon patra vůči bazi

lební, jež současně ovlivňují vertikální mezičelistní vztahy. Ty se výrazně lépe vyvíjely u SS pacientů. Jabbari et al. (2017) rozdíly ve vertikálních mezičelistních vztazích mezi skupinou SS a PP nenachází. Oproti tomu sagitální mezičelistní vztahy se u jejich i našeho souboru v případě obou typů operativy shodně zhoršili. Významný nárůst konvexity měkkého profilu v důsledku výraznější prominence nosu u SS skupiny byl další z významných odlišností mezi oběma skupinami. To je v souladu s nálezy Brattstroma (1991), který popisuje vyšší konvexitu měkkého profilu u SS pacientů, než u skupin s PO. Co se týče dentoalveolární složky, významný rozdíl nalézáme v proklinaci řezáků, a to výrazně ve prospěch SS skupiny. Předchozí studie předpokládají korelaci mezi vyšší proklinací řezáků, ale současně horšími vertikálními mezičelistními vztahy v souvislosti s léčbou fixními aparáty (FA). Náš soubor tyto domněnky nepotvrdil. V rámci SS skupiny bylo léčeno 72% pacientů fixními aparáty, u PP skupiny to bylo o 20% méně, a přesto se vertikální mezičelistní vztahy vyvíjely příznivěji u SS jedinců. Nesignifikantně lepší překus u SS pacientů byl navíc výsledkem celkově vyšší proklinace dentoalveolárního hřebene, nejen proklinace špičáků.

Naše výsledky tedy naznačují, že časný zásah do alveolárního oblouku, jak v případě PO, tak popsaný u našeho PP souboru, celkově negativně ovlivňuje dentoalveolární složku maxily. Patrné je zároveň horší postavení až retroinklinace maxily, na rozdíl od SS jedinců. Obecně můžeme říci, že efekt SS u našeho souboru pacientů nepředstavuje pouze úspěšnější rekonstrukci defektu alveolu, ale manifestuje se také příznivějšími vertikálními mezičelistními vztahy, vyšší proklinací horních i dolních řezáků a vyšší konvexitou měkkého profilu, než je tomu u PP jedinců.

3.4 Vývoj obličeje u dětí v období pubertálního růstu

Studie **Koudelová et al. (2015)** doplňuje předkládanou disertační práci auxologickým pohledem na obličej dospívajících chlapců a dívek ve věku od 12 do 15 let. Soubory zdravých jedinců jsou pro antropologické studie nepostradatelné a to jak z hlediska využití jako srovnávacích souborů při detekci odchylek u patologií, tak z hlediska získání přehledu o růstových změnách v jednotlivých vývojových obdobích. Dílčími cíli této práce bylo: 1) popsat variabilitu tvaru a formy obličeje mezi chlapci a dívkami v jednotlivých věkových kategoriích, 2) definovat rozdíly mezi jednotlivými věkovými kategoriemi a 3) identifikovat sexuálně dimorfní znaky. Soubor tvořilo 30 jedinců (17 chlapců a 13 dívek), kteří byli longitudinálně sledováni v průběhu čtyřletého

časového období. Přístrojové a softwarové vybavení sloužící sběru, úpravě a vyhodnocování dat zahrnovalo faciální skener Vectra 3D, RapidForm XOS software a Morphome3cs software. Obličeje byly hodnoceny jak z pohledu tvaru (odfiltrován vliv velikosti), tak z pohledu formy (tvar + velikost). Prvním krokem bylo zhodnocení variability formy a tvaru u jednotlivých věkových kategorií. U formy začalo být signifikantní odlišení mezi chlapci a dívkami patrné od 14 let věku, v 15 letech se pak rozdíly dále zvýraznily. Separace skupin byla na základě první hlavní komponenty (PC1), která bývá nejčastěji interpretována jako míra velikosti, zatímco ostatní komponenty jsou interpretovány jako míry tvaru (Mitteroecker et al., 2013). Forma obličeje tedy více odráží vývoj sexuálního dimorfismu ve smyslu velikosti znaků než tvaru obličeje. Z pohledu tvaru obličeje se skupiny signifikantně nelišily. Variabilita tvaru byla ve všech věkových kategoriích větší u chlapců a rozdíly mezi pohlavími zde nebyly v průběhu sledovaného období patrné. Naše výsledky jsou v rozporu s Bulygina et al. (2006), která sice na základě longitudinálního hodnocení Rtg snímků popisuje jistou divergenci v růstových trajektoriích od 12 let věku, nicméně 2D hodnocení mají určité limitace a ztrácí se zde informaci o celkovém tvaru.

Rozdíly formy mezi chlapci a dívkami byly následně vizualizovány pomocí konstrukce průměrných obličejů a jejich vzájemné superimpozice. Nepatrně se rozdíly rýsovaly již od nejmladší kategorie, kde bylo patrné delší čelo a prominence orbitální oblasti u dívek. U chlapců naopak prominovaly nadočnicové oblouky a oblast horního rtu. Ve třinácti letech se rozdíly mírně zvýraznily. U dívek byla navíc patrná prominence v oblasti jařmových kostí, u chlapců se zvětšila prominující nasolabiální oblast a začala se prodlužovat výška dolního obličeje. Ve 14 letech u chlapců již signifikantně prominoval nos a oblast horního rtu, u dívek byla v prominenci celá oblast tváří. V 15 letech byla u dívek celkově signifikantní prominence orbitální oblasti a tváří, zatímco u chlapců výrazně prominovala nadočnicová oblast, nos a horní ret. Signifikantní prominence nadočnicové oblasti je typický maskulinní znak, společně s retruzí orbitální oblasti jej u dospívajících chlapců popisuje Toma et al. (2008) u dospělých mužů pak Hennessy et al. (2005). Prominence jařmových kostí a postupně celé oblasti tváří je u dívek během puberty spojena s ukládáním bukálního tuku (Coleman and Grover, 2006), oploštění u chlapců může být také způsobeno celkově širšími jařmovými kostmi a výběžky maxily (Gonzalez et al., 2011). Vůbec nejvýraznější, postupně se rozvíjející rozdíly, byly nalezeny v oblasti nosu, což bylo v souladu s předchozími studiemi (Genecov et al., 1990; Kau and Richmond, 2008;

Toma et al., 2008). Dle hypotézy autorů Rosas & Bastir (2002) koreluje velikost nosu a nostril u mužů s vyššími požadavky na příjem kyslíku. Celkově větší a delší nos chlapců souvisí také s prominencí horního rtu (Kau and Richmond, 2008; Toma et al., 2008). Po 13 roce se u chlapců také začíná prodlužovat výška dolního obličeje, což je dáno výrazným růstem mandibuly během pubertálního spurtu (Ferrario et al., 1999; Bulygina et al., 2006). Závěrem můžeme shrnout, že mezi 12. a 15. rokem nebyl na základě metod 3D geometrické morfometrie prokázán pohlavní dimorfismus tvaru obličeje, zatímco pohlavní dimorfismus formy obličeje se signifikantně odlišoval od 14 let věku.

4 Závěr

V této disertační práci byla hodnocena role neonatální cheiloplastiky a sekundární spongioplastiky ve vývoji obličeje pacientů s orofaciálními rozštěpy. Jedním z cílů bylo alespoň částečně přispět k odpovědi na otázku, zda má neonatální cheiloplastika negativní vliv na růst jednotlivých obličejových struktur v určitých etapách vývoje předškolního dítěte. Z našich výsledků vyplývá, že u pacientů s kompletními jednostrannými rozštěpy i s jednostrannými rozštěpy s mostem není během prvních deseti měsíců po cheiloplastice předozadní růst patra limitován. Šířka rozštěpové štěrbiny se snižuje v závislosti na typu a závažnosti vady vlivem kombinace modelačního efektu sutury rtu na postižený dentoalveolární oblouk a současného růstu obou segmentů v anteriorních oblastech. Vyloučili jsme zmenšování rozštěpové štěrbiny na základě často popisovaného nežádoucího zúžení přední dentoalveolární šířky horní čelisti, kdy tento parametr zůstává u našich jedinců v závislosti na typu vady buď beze změny, nebo se mírně zvyšuje. Signifikantní růst byl nalezen u obou typů vady i v posteriorních oblastech. Variabilita jedinců s kompletním postižením se během prvního roku života snižuje a současně se přibližuje variabilitě méně postižených jedinců. To značí, že růst patra sledovaných dětí procházel stejnými změnami a sledoval podobný růstový trend. Z porovnání s daty později operovaných jedinců a kontrolních souborů vyplývá, že růstový trend horní čelisti má u našich pacientů charakter spíše se blížící normě než pozdní operativě.

Hlavní odchylky v morfologii obličeje nalezené u předškolních dětí s rozštěpem odpovídají standardně popisovaným odchylkám rozštěpových pacientů. Nejvýraznější odchylky od normy byly nalezeny u pacientů s oboustranným kompletním rozštěpem, méně výrazné pak byly u pacientů s kompletním jednostranným rozštěpem. U obou skupin se týkaly zejména nasolabiální oblasti, tedy struktur přímo zasažených rozštěpem, ale zároveň byla patrná signifikantní retruze laterálních oblastí horní čelisti. Nejméně postiženými a normě celkově nejvíce podobnými jedinci byla skupina pacientů s izolovaným rozštěpem rtu, kde nebyly laterální oblasti zasaženy. Tato zjištění naznačují, že na růst zdravé maxily nemá časná sutura rtu negativní vliv. Pokud zohledníme poznatky o růstu postižené horní čelisti popsané v předchozí části a také informace o tom, že maxila je u kompletních rozštěpových vad kratší již před prvním chirurgickým zákrokem, nemá NCH celkově výrazně inhibiční vliv na růst horní čelisti

rozštěpových pacientů. Podporou tohoto tvrzení může být i fakt, že v předškolním věku nenacházíme u významných rozštěpových odchylek signifikantní progresi s věkem.

Odchylky od perfektní symetrie byly u všech skupin pacientů i u normy nalezeny v oblasti čela, shodně s pozitivními hodnotami vpravo. Vzhledem k těmto okolnostem neshledáváme souvislost asymetrie čelní oblasti s rozštěpovou vadou, ale považujeme ji za následek polohové plagiocefalie a z ní pramenící prominence čela. Nejvýraznější projevy asymetrie byly přítomny v oblastech přímo související s rozštěpem, avšak u kompletních vad se asymetrie vyskytovala i laterálně v oblasti maxily. Tyto výsledky naznačují, že kompletní vady s postižením patra rozvíjejí asymetrii i laterálně od samotného místa postižení měkkých tkání, zatímco nepřítomnost asymetrie laterálních oblastí u UCL jedinců naznačuje, že izolovaný rozštěp rtu v kombinaci s NCH nezpůsobuje významnou asymetrii oblastí obličeje. S výjimkou horní labiální oblasti se oboustranné rozštěpy charakterem asymetrie blížily spíše normě, než jednostranným rozštěpům. Až na výjimku nesignifikantní progrese asymetrie v oblasti tváří u kompletních vad, asymetrie v ostatních oblastech se s věkem nezvýraznila.

Pokud se týká řešení defektu alveolu, naše výsledky naznačují, že pacienti operovaní sekundární spongioplastikou vykazovali během pubertálního růstu výrazně lepší vývoj vertikálních mezičelistních vztahů a zároveň větší proklinaci horních i dolních řezáků. Současně byla na konci sledovaného období přítomna také větší konvexita měkkého profilu, což je jedním z významných cílů, kterých se celková léčba pacientů s rozštěpem snaží z estetického hlediska dosáhnout. Časný zásah do alveolárního oblouku, v případě dříve prováděné primární osteoplastiky či u našeho souboru pacientů operovaných primární periosteoplastikou, naopak celkově negativně ovlivňoval dentoalveolární složku maxily a její postavení vzhledem k bazi lební, kde byla nalezena retroinklinace. V dalších parametrech, jako je délka maxily či sagitální mezičelistní vztahy, se obě skupiny nelišily.

Během pubertálního vývoje u zdravých jedinců nebyl do 15 let věku prokázán signifikantní pohlavní dimorfismus tvaru obličeje. Pohlavní dimorfismus formy se postupně zvýrazňoval a signifikantně odlišný byl až od 14. roku, přičemž forma obličeje představovala vývoj sexuálního dimorfismu více ve smyslu velikosti znaků než tvaru obličeje. Významné rozdíly byly v prominenci nadočnicové oblasti, nosu a horního rtu u chlapců, u dívek naopak prominovala oblast orbit a tváří.

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Přílohy

A. Seznam předkládaných publikací

1. Palatal growth in complete unilateral cleft lip and palate patients following neonatal cheiloplasty: Classic and geometric morphometric assessment

Eva Hoffmannova, Šárka Bejdová, Jiří Borský, Ján Dupej, Veronika Cagáňová, Jana Velemínská

International Journal of Pediatric Otorhinolaryngology 2016; 90:71-76. (IF 1.159)

2. Three-dimensional development of the upper dental arch in unilateral cleft lip and palate patients after early neonatal cheiloplasty

Eva Hoffmannova, Veronika Moslerová, Ján Dupej, Jiří Borský, Šárka Bejdová, Jana Velemínská

International Journal of Pediatric Otorhinolaryngology 2018, accepted. (IF 1.159)

3. Three-dimensional evaluation of facial morphology in pre-school cleft patients following neonatal cheiloplasty

Martina Dadáková, Veronika Cagáňová, Ján Dupej, Eva Hoffmannová, Jiří Borský, Jana Velemínská

Journal of Craniomaxillofacial Surgery 2016; 44(9): 1109-16. (IF 1.583)

4. Three-dimensional assessment of facial asymmetry in preschool patients with orofacial clefts after neonatal cheiloplasty

Veronika Moslerová, Martina Dadáková, Ján Dupej, Eva Hoffmannova, Jiří Borský, Miloš Černý, Přemysl Bejda, Karolína Kočandrlová, Jana Velemínská

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5. Facial growth and development in unilateral cleft lip and palate: Comparison between secondary alveolar bone grafting and primary periosteoplasty

Veronika Cagáňová, Jiří Borský, Zbyněk Šmahel, Jana Velemínská

Cleft Palate Craniofacial Journal 2014; 51(1): 15-22. (IF 1.238)

6. Development of facial sexual dimorphism in children aged between 12 and 15 years: A three-dimensional longitudinal study

Jana Koudelová, Jaroslav Brůžek, Veronika Cagáňová, Václav Krajíček, Jana Velemínská

Orthodontic & Craniofacial Research 2015; 18(3): 175-84. (IF 1.64)

B. Příspěvky na mezinárodních konferencích

1. Orofaciální růst a vývoj u pacientů s celkovým jednostranným rozštěpem rtu a patra (UCLP) po sekundární spongioplastice: srovnávací studie.

Cagáňová V, Šmahel Z, Velemínská J

Antropologické dny v Budmericiac, Červen 2010, Budmerice; přednáška

2. Three-dimensional longitudinal growth analysis of facial morphology in children from 12 to 15 years old.

Koudelová J, Cagáňová V, Krajíček V, Velemínská J

3° International Conference on Human and Social Sciences, September 2013, Rome; poster

3. Palatal growth in complete unilateral cleft lip and palate patients following neonatal cheiloplasty.

Hoffmannova E, Bejdova S, Borsky J, Dupej J, Caganova V, Veleminska J

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Palatal growth in complete unilateral cleft lip and palate patients following neonatal cheiloplasty: Classic and geometric morphometric assessment

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ABSTRACT

Background: A new method of early neonatal cheiloplasty has recently been employed on patients having complete unilateral cleft lip and palate (cUCLP). We aimed to investigate (1) their detailed palatal morphology before surgery and growth during the 10 months after neonatal cheiloplasty, (2) the growth of eight dimensions of the maxilla in these patients, (3) the development of these dimensions compared with published data on noncleft controls and on cUCLP patients operated using later operation protocol (LOP; 6 months of age).
Methods: Sixty-six virtual dental models of 33 longitudinally evaluated cUCLP patients were analysed using metric analysis, a dense correspondence model, and multivariate statistics. We compared the palatal surfaces before neonatal cheiloplasty (mean age, 4 days) and before palatoplasty (mean age, 10 months).
Results: The palatal form variability of 10-month-old children was considerably reduced during the observed period thanks to their undisturbed growth, that is, the palate underwent the same growth changes following neonatal cheiloplasty. A detailed colour-coded map identified the most marked growth at the anterior and posterior ends of both segments. The maxilla of cUCLP patients after neonatal cheiloplasty had a growth tendency similar to noncleft controls (unlike LOP).
Conclusions: Both methodological approaches showed that early neonatal cheiloplasty in cUCLP patients did not prevent forward growth of the upper jaw segments and did not reduce either the length or width of the maxilla during the first 10 months of life.

1. Introduction

Orofacial clefts are among the most common craniofacial deformities [1–3] and are associated with serious orthodontic anomalies [4]. The incidence in the Czech Republic is approximately 1:530 of living newborns. Their background is multifactorial, in other words, orofacial clefts are caused by a combination of genetic and environmental factors [5]. They are the result of hypoplasia of facial prominences and palatal shelves and growth restriction of the mandible [6]. This malformation emerges from approximately the fourth to the eighth week of prenatal development. The range of the affliction varies, being localised to the lip, upper jaw, and palate, separately or in different combinations [1]. Complete unilateral cleft lip and palate (cUCLP), the subject of our study, is the most common type of orofacial cleft [7,8].

Treatment of cleft patients should begin as soon as possible [9] and includes surgical repair of the cleft lip, cleft palate, affected nose, along with orthodontic therapy [7]. The surgical treatment goals are mainly to restore the form and function of structures affected by clefting [10] and thus improve facial appearance and, ultimately, influence the psychological impact on the child and

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family [9]. The associated treatment goals are to improve speech and food intake [11].

Primary cheiloplasty is necessary to reconstruct the normal anatomy and function of the lip [12], and the most common age for surgical treatment is between 3 and 6 months [13,14]. Cheiloplasty can also be performed during the first week of life, and it is becoming the most common surgical approach in the Czech Republic. Neonatal cheiloplasty is believed to result in many benefits such as excellent wound healing, feeding facilitation [9,11,13], and reducing the psychological impact on family [15]. The question is whether neonatal cheiloplasty results in a better or the same outcome as the later operation protocol (LOP). We evaluated the isolated influence of neonatal cheiloplasty on maxillary growth during the first 10 months after lip surgery. We compared maxillary morphology before and 10 months after neonatal cheiloplasty using classical morphometry combined with three dimensional (3-D) geometric morphometric methods. The aim of our study was to determine whether neonatal cheiloplasty has any negative effect on the growth of the maxillary segments during the observed period. We compared our morphometric data with published data on noncleft controls and cUCLP patients operated using the LOP to prove our hypothesis.

2. Materials and methods

This study was based on morphometric analysis of plaster models of the maxillae of 33 patients with cUCLP. All the patients were of Czech origin and were operated within the first week of life by the same surgeon using the modified Tennison technique. The consent for experimentation with human subjects was obtained. The mean age of the 33 patients who underwent early neonatal cheiloplasty was 3.8 ± 2.7 days, and the mean age for palatoplasty was 10.1 ± 1.8 months. Two plaster casts were taken of each patient, the first before cheiloplasty (T0) and the second before palatoplasty (T1). The plaster casts were scanned using a Breuckmann SmartScan scanner (Aicon 3D Systems GmbH, Braunschweig, Germany) with a resolution of 0.1 mm. The resulting meshes were edited and decimated using RadpidForm XOS software (Inus Technology Inc, Seoul, South Korea).

The first step before any morphometric analysis was to place 11 landmarks on each model in Morphome3cs software (www.morphome3cs.com; Fig. 1). Landmark placement error was determined according to the method of von Cramon-Taubadel et al. (2007) [16], at 0.1665 mm. We used those 11 landmarks to analyse changes in seven linear measurements and one angular measurement during the first 10 months: 1–7 (alveolar cleft width), 5–9 (intermolar width), 4–8 (intercanine width), 4–6 (molar region length on the noncleft side), 8–10 (molar region length on the cleft side), 6–10 (intertuberosity width), 2–11 (palatal length), and ∠1-3-7 (anterior basal angle). Some of the measured dimensions were compared with published data of a noncleft control group [17] and with an LOP group (cheiloplasty at 6 months of age) [18]. We used Wilcoxon's paired signed-rank test to determine whether growth in the specified dimensions was statistically significant. Significance was decided to be at level $\alpha = .05$.

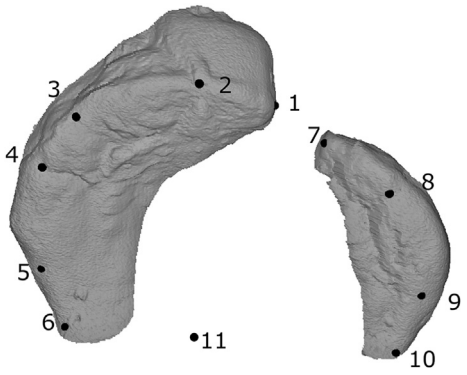

Fig. 1. Reference points on maxillary segments. 1: Most distal point on the edge of the segment on noncleft side; 2: tip of ridge on the line between the labial frenulum and incisive papilla; 3: mesial margin of canine swelling on noncleft side; 4: distal margin of canine swelling on noncleft side; 5: distal margin of molar swelling on noncleft side; 6: tuberosity point on noncleft side; 7: most mesial point on the edge of the alveolar segment on cleft side; 8: distal margin of canine swelling on cleft side; 9: distal margin of molar swelling on cleft side; 10: tuberosity point on cleft side; 11: reference point on the base of the perpendicular line from reference point 2 to the line segment of reference points 6 and 10.

We then analysed the palatal shapes in their entirety using coherent point drift dense correspondence analysis (CPD-DCA) [19]. This is an algorithm that transfers the topology of one surface, called the base, to all the other surfaces. In effect, homologous samplings of these surfaces are generated, allowing for landmark-style statistics and visualisations. CPD-DCA first uses an automatic nonrigid registration algorithm to deform the base mesh onto each nonbase surface, bringing anatomically similar locations into close proximity. Next, closest-point search is used to find corresponding points on the nonbase surface, which are used to resample the nonbase surface. These homologous samplings of each surface are then aligned with generalised Procrustes analysis (GPA) [20]. Note that size was not normalised during GPA and, as a result, the real form of the individuals was analysed. Dimension reduction is accomplished using principal component analysis (PCA); the shape variables reduced to the first two principal components were plotted in a scatter plot. The mean growth direction in the space of the first two principal components was calculated as, where n is the number of specimen pairs and $\boldsymbol{b_i}$ and $\mathbf{a}_i$ are the principal component (PC) scores of the i-th individual after and before surgery, respectively.

Finally, mean shapes for pre- and postsurgery patients were calculated using means of their corresponding vertex coordinates. Average growth pattern was calculated as the average corresponding vertex displacement between pre- and postsurgery surfaces. This mean displacement was visualised by colour-coding the groupwise mean surfaces.

3. Results

3.1. Classical metric analysis

Seven linear and one angular dimension of the maxilla of cUCLP patients were compared between two age groups (T0, T1), one at age 3.8 days and the second at age 10.1 months (Table 1). All the measured dimensions were compared by Wilcoxon signed-rank test. Table 1 shows significant growth increments in all the measured dimensions except intercanine width (4–8), whose size change was not statistically significant. There was an evident decrease in the dimensions associated with convergence of the anterior ends of the upper jaw segments such as cleft width (1–7) and anterior basal angle (1-3-7). On the contrary, there was a significant growth change in the posterior area of upper jaw segments: increase of intertuberosity width (6–10), intermolar width (5–9), and molar region length on the cleft side (8–10) and noncleft side (4–6). There was also a significant growth extension in palatal length (2–11).

A further important aim of our study was a metric comparison (intercanine width, intertuberosity width, and palatal length) of our data with noncleft controls [17] and with another UCLP-patient group operated using a classical LOP [18] (Fig. 2). Initial

Table 1
Testing of changes in linear (mm) and angular (°) measurements during first year of life in cUCLP patients.

Cleft type	cUCLP		p value
Age	1 week	10 months	
Dimension	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
1–7	9.4 ± 4.2	4.1 ± 2.3	***
8–10	15.7 ± 1.9	20.3 ± 1.9	***
5–9	35.7 ± 1.9	38.7 ± 2.4	***
4–8	30.7 ± 2.7	30.7 ± 2.6	NS
4–6	15.4 ± 2.0	19.1 ± 1.9	***
6–10	33.3 ± 1.8	36.1 ± 2.3	***
2–11	22.9 ± 2.3	25.8 ± 2.4	***
1-3-7	20.1 ± 9.5	9.1 ± 5.4	***

*** $p \leq 0.001$.
NS (not statistically significant).

intertuberosity and intercanine widths were larger in both cleft groups compared with the noncleft group because of a gap between palatal segments. Intertuberosity width in our neonatal cheiloplasty group showed a growth tendency more similar to the noncleft control group compared with the LOP group. Palatal length exhibited a similar growth tendency in both cleft groups and the noncleft group. Intercanine width, as one of the most important indicators of surgical impact, showed a growth trend more similar to the noncleft group than to the LOP group. Our results show that intercanine width did not change during the observed period, unlike the control group, wherein that dimension increased in size. On the contrary, the LOP group showed a decrease of this dimension following surgery.

Overall, we did not find any significant growth disturbance in any of the measured dimensions. Moreover, intertuberosity width and palatal length dimensions share growth patterns similar to the control group.

3.2. Geometric morphometric evaluation of maxillary surface morphology

Maxillary surface variability in patients with cUCLP was analysed by performing principal component analysis (PCA) on the respective form variables. Surface differences of the maxillary segments between the two age groups were characterised using the first two principal components (PC1, PC2) (Fig. 3). Out of the total form variability, PC1 explained 51.1%, and PC2, 15.3%. Each specimen appears twice in the plot, at age T0 and at age T1. Projections of each specimen at T0 and T1 into the first two principal components were plotted in a scatterplot. Overall, the variation of maxillary form was greater in the neonatal group (T0). The effect of PC1 and PC2 on the shape of the maxillary segments was visualised using colour-coded maps (Fig. 3). Mostly size was manifested in PC1. An increase in PC1 score from negative to positive values translates into an enlargement of maxillary segments (red colour indicates a vertex moving outward, while blue shows an inward motion). The mean of the T1 group was shifted toward positive scores of PC1, which would indicate that the maxillary segments were larger in T1 than in T0. An increase in the PC2 score corresponded to the increase of palatal length and convergence of both segments at the anterior ends of both segments. Upper jaw segments in T1 were larger, with a smaller anterior cleft gap. The direction of ageing trajectories is displayed by the arrow and shows the growth change in the time interval T0–T1. Altogether, the maxillary segments were growing in all directions and the anterior cleft width was reduced.

Using the CPD-DCA analysis, we modelled the growth of the maxillary segments in the cUCLP patients during the first 10 months after birth by colour-coded maps. Areas of the greatest growth were marked red (Fig. 4). The results show a major growth pattern located at the anterior and posterior ends. Growth of the maxillary segments was generally more pronounced on the lateral circumference of both segments. Both separated segments were growing in size, prolonging and converging in the anterior ends of the segments. On the contrary, the posterior ends of both segments did not show any convergence.

4. Discussion

It has been reported that neonatal cheiloplasty has many benefits concerning good aesthetic outcome, and socialisation of child with family [9,13]. To evaluate the independent effect of neonatal cheiloplasty, we analysed the growth of the maxilla during the first 10 months of life, that is, before palatoplasty.

The combination of 2-D and 3-D analysis showed the growth pattern of the maxillary segment and the growth tendency of cUCLP patients. The results showed that neonatal cheiloplasty did not prevent growth in the anterior part of either segment and that our data shared a growth tendency in observed width dimensions more similar to the control group [17] than to the LOP group [18]. The palatal length dimension had a growth trend similar to both the neonatal and LOP cUCLP groups, also to the control group.

4.1. Growth of the upper jaw segments

Clefting of the maxilla causes retardation of growth, but the initial width dimensions such as intercanine width and intertuberosity width were larger than in the noncleft patients. More growth retardation was visible in the palatal length dimension than in the noncleft group. Also, previous studies have described palatal length as less than in noncleft patients and intercanine and intertuberosity width as more than in noncleft patients [17,21]. Growth changes in maxillary segments have been shown in many studies concerning an LOP (3–6 months) [17,18,22–24]. Those studies reported the same results shown in our study; that the intertuberosity width and palatal length increased significantly in the months following cheiloplasty.

The intertuberosity width in our neonatal cheiloplasty group showed an increasing growth trend after surgery, that is, the dimension increased significantly during the observed period. The same growth trend was shown in the noncleft control group. Overall, the initial intertuberosity width in both cheiloplasty protocol groups was larger than in the noncleft patients and shows an increasing growth trend after cheiloplasty. Our results are supported by many studies [17,22,23,25–27], in which cUCLP patients were operated by LOP.

We also observed palatal length growth trends in different operation protocol groups and in the noncleft group. The palatal length growth trend exhibited by the course of the curve in our data was similar to that of the LOP and noncleft control group. The initial palatal length in the noncleft control group was larger than in our cUCLP data. The same results were described by Kramer et al. (1994, 1996), wherein different cleft types were compared with the control group and smaller initial palatal length was apparent only in the cUCLP group.

Our data showed no significant change in intercanine width after neonatal cheiloplasty and the size of this dimension stayed the same during the first 10 months. The same results were documented by Braumann et al. (2003), in which both cleft groups were operated using the same surgical procedure—the method of Tennison—but the surgery timing was different and was performed by different surgeons. Our results showed a constant growth trend

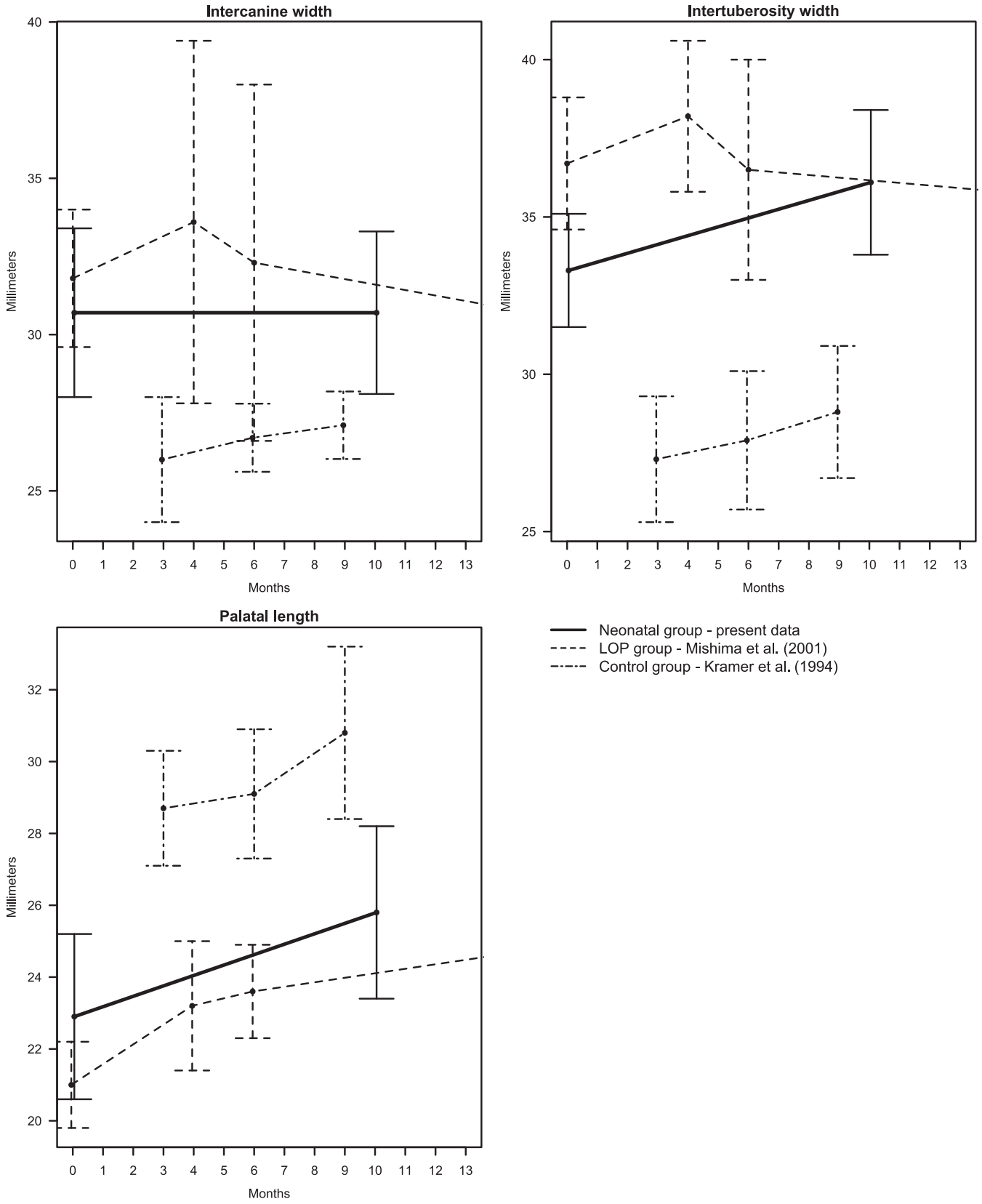

Fig. 2. Comparison of growth trends of maxilla in cleft and noncleft groups. Three mean linear maxillary dental arch measurements were taken at different ages (*x*-axis) and demonstrate corresponding size of the maxilla (*y*-axis) in cUCLP early neonatal cheiloplasty group, cUCLP later operation protocol group, and control group. Neonatal cheiloplasty data were compared with data published on LOP group and control group, intercanine width, intertuberosity width, and palatal length.

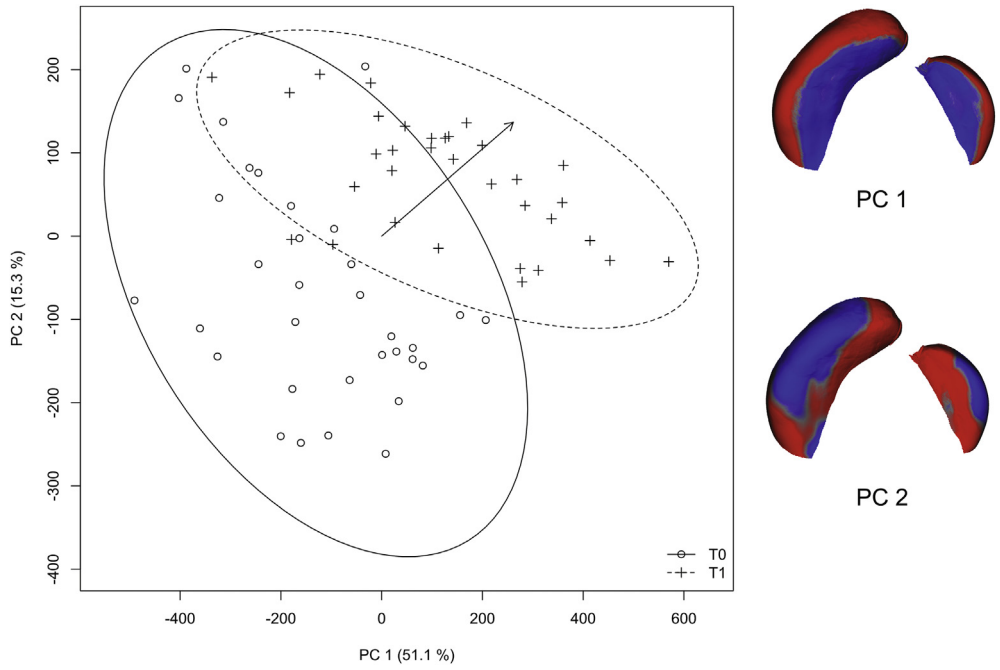

Fig. 3. Shape variability of cUCLP patient in two age categories described by PC1 and PC2. Specimen appears twice, first, during the first week of life (age 0), and second, at 10 months (age 1). Confidence ellipses for groups at 95% level were included. Colour-coded maps visualise the effect of each principal component (PC) on growth of the maxilla. Red areas increase outward with age, while blue areas increase inward. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

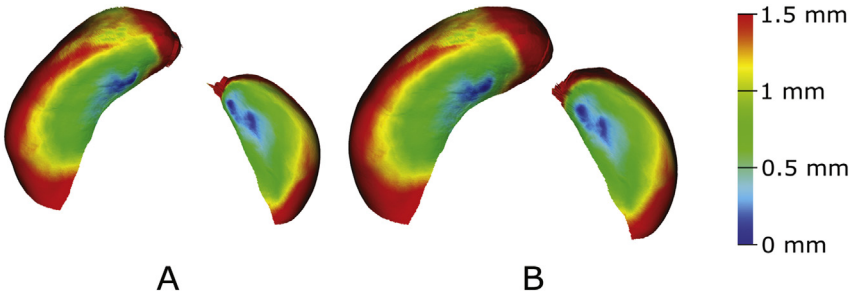

Fig. 4. Visualisation of growth of the maxillary arch in the first year of life in cUCLP. A: Mean 3-D model before early neonatal cheiloplasty at age 3.8 days. B: Mean 3-D model at 10.1 months. Growth of particular parts of the maxilla are visualised by colour-coding the mean mesh.

in intercanine width in the neonatal cheiloplasty group that was more similar to the noncleft group, which showed a small increase during the first months of life. However, the LOP group showed a decreasing trend following cheiloplasty. The decreasing growth trend described in patients operated by LOP is widely supported by several studies [17,22–24]. The decrease of intercanine width following cheiloplasty could have been caused by surgery timing, because the moulding effect of neonatal cheiloplasty did not allow the separated segments to expand in the transverse dimension.

4.2. Geometric morphometric evaluation of maxillary surface morphology

Our results suggest that the form variability was higher in the cUCLP patients in the neonatal period (T0) than 10 months after cheiloplasty (T1). It is known that there is more variability in maxillary form in cleft patients than in the noncleft population [28,29]. The moulding effect of cheiloplasty resulted in a decrease of alveolar cleft width (1–7) and therefore in reduction of form variability.

Our data also showed distinct growth in both the anterior and posterior ends of the upper jaw segments after neonatal cheiloplasty. Similar results were described by Huang et al. (2002) in patients operated by an LOP at 3 months of age. These results imply that cheiloplasty did not prevent posterior growth of the upper jaw segments whether the operation was performed during the neonatal period or at 6 months. Other studies [17,21,23,30] have described growth in the posterior ends of the upper jaw segments, but not in the anterior parts.

It is apparent that the reduction in alveolar cleft width reported by many studies [17,18,24,31] was affected by the pressure of the repaired lip. Contrariwise, our data showed that this reduction was caused by a combination of the moulding effect of the repaired lip and also by growth localised at the anterior ends of both upper jaw segments. Our data also showed no significant change in intercanine width, so it is apparent that the reduction of alveolar cleft width was not caused by narrowing of the upper jaw arch.

It is important to continue the study of the same cUCLP patients in the future, because the resulting favourable development could be discontinued by palatoplasty, which can disrupt the palatal

growth pattern.

5. Conclusion

The aim of our study was to evaluate growth changes in cUCLP patients after cheiloplasty and to compare the results with published data of noncleft patients and patients operated by the LOP (at 6 months). Both width and length dimensions—except intercanine width—increased significantly during the 10 months postsurgery. Important growth concerned the anterior and posterior ends of both upper jaw segments, and growth was more pronounced in the noncleft upper jaw segment. Anterior growth combined with the formative effect of the reconstructed lip resulted in a reduction in anterior cleft width and a consequent reduction of the upper jaw defect. The maxillary segments 10 months after neonatal cheiloplasty in cUCLP patients shared almost the same growth tendency as noncleft controls.

Based on our findings, we were unable to prove that neonatal cheiloplasty causes any reduction in size of the separated segments. Overall, the growth tendency was more similar to noncleft patients than to patients operated by the LOP.

Conflict of interest

There are no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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Three-dimensional development of the upper dental arch in unilateral cleft lip and palate patients after early neonatal cheiloplasty

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ABSTRACT

Objectives: This prospective morphometric study evaluated the growth of the upper dental arch in UCLP patients after early neonatal cheiloplasty and compared the selected dimensions with published data on non-cleft controls and on later operation protocol patients.

Methods: The sample comprised 36 Czech children with nonsyndromic complete UCLP (cUCLP) and 20 Czech children with nonsyndromic incomplete UCLP (UCLP + b). 2-D and 3-D analyses of palatal casts were made at two time points: before neonatal cheiloplasty at the mean age of 3 days (± 1 day), and 10 months after surgery at the mean age of 10 months (± 1 month).

Results: The upper dental arch of cUCLP and UCLP + b patients showed similar developmental changes, but the cleft type influenced growth significantly. The initial high shape variability in cUCLP patients diminished after 10 months, and approached the variability in UCLP + b patients. Both the width and length dimensions increased after surgery. Important growth concerned the anterior ends of both segments. The width and length dimensions illustrated similar growth trends with non-cleft controls and UCLP patients who underwent later cheiloplasty.

Conclusion: Early neonatal cheiloplasty caused no reduction in the length or width dimensions during the first year of life. Our data suggest a reconstructed lip has a natural formative effect on the actively growing anterior parts of upper dental arch segments, which cause narrowing of the alveolar cleft.

1. Introduction

Orofacial clefts are associated with serious developmental anomalies of both hard and soft tissues [1–4]. The growth disturbance of the maxilla is typical in UCLP patients [5] and is suspected to result from congenital hypoplastia, and growth deficiency caused by scar formation resulting from lip or palatal repair [6].

Treatment of cleft patients starts with surgical repair of the cleft lip and/or palate with special attention to the soft tissues of the lip and nose [7,8]. The repair of the lip physiologically restores the continuity of the upper lip musculature [9]. Nowadays, cheiloplasty is performed more and more often in neonates during the first week of life, but widely accepted timing for surgical treatment is still between 3 and 6 months of age [10,11]. Such neonatal cheiloplasty solves the problems resulting from the cleft lip as soon as possible. The essential motive for proposing neonatal surgery is the psychosocial impact on mother – baby interaction and other family members [11–13]. Benefits of neonatal cheiloplasty include outstanding wound healing with barely visible scars, facililiation of feeding, child socialisation, and dealing with OME (otitis media effusion) [9,10,12,14,15]. It is argued that the later operation protocol (LOP) – performed between 3 and 6 months of age – yields better aesthetic results since the postnatal increase in size of anatomic structures allows their easier accessibility and manipulation during surgery [16], but early neonatal cheiloplasty performed by an experienced surgeon has similar aesthetic and orthodontic results [17].

Treatment outcome and favourable or unfavourable growth of upper dental arch can be also anticipated according to the initial severity of the cleft deformity [18] where patients having a small alveolar cleft develop a more protruded (i.e., less hypoplastic) maxilla than those with a large alveolar cleft [19].

A new method (a modification of the method of Tennison) has recently been employed for surgical repair of unilateral cleft lip in newborns with UCLP operated during the first week of life [9]. The

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modification consists of using two tissue flaps from the margins of the cleft lip to deepen the oral vestibule (VF) and floor of the nasal vestibule and to bring extra tissue to the suture region (NF).The Tennison's flap was used to complete the shortened philtrum on the cleft side. This provides a suture with minimum tension of the lip tissue after surgery. The orbicularis oris muscle was isolated and nasal septum was repositioned. The rotated and dislocated nasal alar cartilage on the cleft side was released and its position and shape corrected. .A more detailed description of neonatal cheiloplasty was published in our previous report [14].

The aim of our current study is to evaluate and compare growth of the upper dental arch in patients with different cleft types before and after neonatal cheiloplasty using two-dimensional (2-D) and three-dimensional (3-D) methods.

2. Patients and methods

This prospective study is part of a long-term research project focused on the influence of neonatal cheiloplasty on growth and development of the face. The study was based on morphometric analysis of plaster casts of the upper dental arch of 56 patients of Czech origin with nonsyndromic UCLP: 36 of the patients had complete UCLP (cUCLP) and 20 patients had UCLP with either a soft or a combined tissue bridge (UCLP + b). The soft and combined tissue bridge groups were grouped together, since no significant differences between the groups were found. The persisting tissue bridge is located at the lower margin of the nostril and soft tissue and skeletal bridge across the anterior maxilla. The soft tissue adhesions connect the divided maxillary fragments in the absence of the bony union of the maxillae at the cleft side.

Two plaster casts were available for each patient, one taken before cheiloplasty at the mean age of 3 days (± 1 day) - age 0, the other at the mean age of 10 months (± 1 month) - age 1. The plaster casts were made under anesthesia. The surgery was performed by the same surgeon within the first week of life.

The plaster casts were scanned using a Breuckmann SmartScan scanner (Aicon 3D Systems GmbH, Braunschweig, Germany) with a resolution of 0.1 mm. The meshes were edited using RapidForm XOS software (INUS Technology, Inc, Seoul, Korea).

Morphometric analysis was based on 11 landmarks that were placed on each model according to a modified approach developed by Mazaheri et al. [20] (Fig. 1). Furthermore, six linear measurements and one angular measurement were taken: 1–7 (alveolar cleft width), 5–9 (inter-molar width), 4–8 (intercanine width), 4–6 (molar region length on the noncleft side), 8–10 (molar region length on the cleft side), 6–10 (intertuberosity width), ∠1–3 – 7 (anterior basal angle), and 2–11 (palatal length). Landmark placement and all further processing was performed using Morphome3cs software (www.morphome3cs.com). Landmark placement error was determined [21] at 0.15 mm.

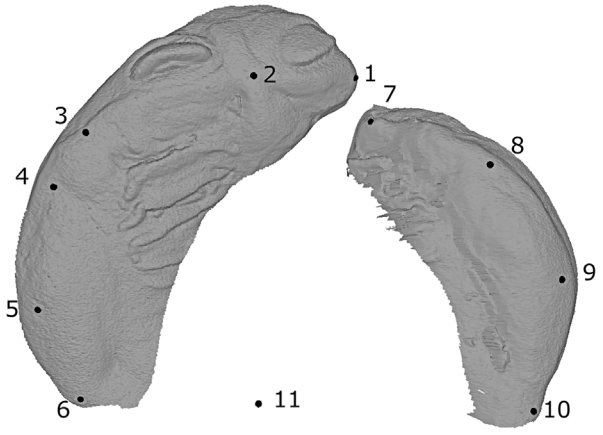

Fig. 1. Reference points on the alveolar arch. 1- the most distal point on the edge of the alveolar segment on the noncleft side; 2 - tip of the ridge on the line between labial frenulum and incisive papilla; 3 - mesial margin of canine swelling on the noncleft side; 4 - distal margin of canine swelling on the noncleft side; 5- distal margin of swelling of the molar swelling on the noncleft side; 6 - tuberosity point on the noncleft side; 7 – the most mesial point on the edge of the alveolar segment on the cleft side; 8 - distal margin of canine swelling on the cleft side; 9 - distal margin of molar swelling on the cleft side; 10 - tuberosity point on the cleft side. 11- reference point on the base of the perpendicular line from reference point 2 to the line connecting segment of reference points 6 and 10.

In order to evaluate changes in size during the studied period, the differences in measurements and the post-treatment changes in dimensions between cleft types (cUCLP and UCLP + b) were tested using Student's t-test. Statistical significance was decided at $\alpha = 0.05$.

Both cUCLP and UCLP + b groups were further subdivided by cleft severity inferred from cleft width at age 0, into three subgroups: mild (0–5 mm, N = 22), moderate (5–10 mm, N = 16), and severe (> 10 mm, N = 18). Two-way analysis of variance (ANOVA) was used to verify the effect of cleft type (cUCLP or UCLP + b) and cleft severity (mild, moderate, severe) on the measurements. We also tested the interaction between the two factors. The differences between the specified measurements before and after treatment in both cleft groups were used as the dependent variable.

Selected dimensions were compared to those of non-cleft control groups and UCLP patients operated following the LOP (3–6 months of age). The control group data and the data of the later cheiloplasty groups were taken from Kramer et al. [22].

In order to perform statistical analysis on the surface data, vertex homology among the meshes had to be created; the following outlines the applied procedure. We used dense correspondence analysis (DCA), described by Hutton et al. [23], which transfers the topology of an arbitrarily-selected base mesh to all other meshes. In effect, all meshes were resampled in a way that creates homologous vertices, which can be treated as landmarks in further processing; therefore, they are dubbed quasilandmarks. Note, that before further processing, all surfaces were aligned to a common mean, using generalized Procrustes analysis (GPA) on their landmarks.

Principal component analysis (PCA) was performed on the quasi-landmark coordinate matrix to reduce the dimensions of the data, while simultaneously minimizing the loss of information. The transformed specimens and confidence ellipses denoting group variability for both cleft types and ages were visualized in a PCA scatter plot.

Taking advantage of the availability of two plaster casts for each patient (taken in the first week and at 10 months of age), we modelled the longitudinal growth of the upper dental arch in each cleft type (cUCLP and UCLP + b) during the first 10 months after early neonatal cheiloplasty. The registered vertex coordinates of pre- and post-treatment stages were subtracted, which produced the growth displacement fields. The mean growth was visualized as a colour map along with pre- and post-treatment mean surfaces. Colour encodes the distance travelled by each particular feature during growth, with blue denoting little growth, and red indicating extensive growth.

3. Results

3.1. Shape variability

Shape variability of the upper dental arch in patients with cUCLP and UCLP + b was analysed by PCA of the respective shape variables. Their scores in the first two principal components (PC1, PC2) are showen in a scatter plot (Fig. 2). The shape variation explained by PC1 is 28.8% and 10.7%. by PC2. Each specimen appears twice in the plot: first, at age 0 and second, at age 1. The shape variability of the more serious cleft type (cUCLP) group at age 0, is notably larger than in the other three groups. The shape difference between cUCLP and UCLP + b at age 0 is mostly explained by PC1. Ten months after surgery, the shape variability of both cleft types decreased considerably. PC1 shows the decrease in alveolar cleft width and in shape variability of the upper dental arch, both of which are more apparent in the cUCLP group than

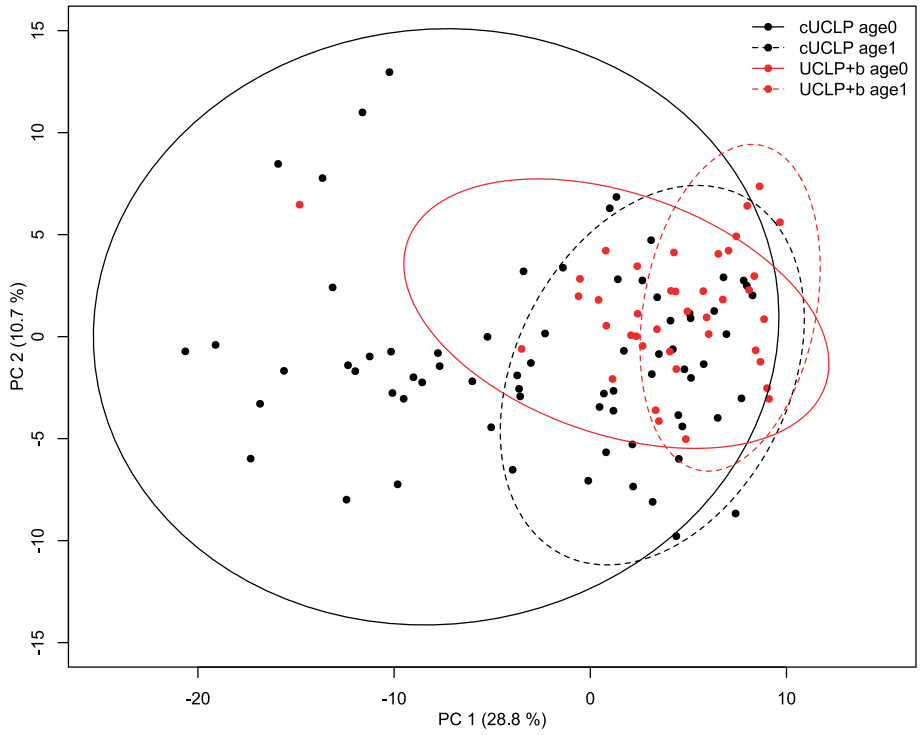

Fig. 2. Shape variability of both cleft groups in 2 age categories described by PC1 and PC2. Each specimen (cUCLP, UCLP + b) appears twice, i.e., first, during the first week of life (age 0), and second, at approximately age of 10 months (age 1). Confidence ellipses for groups at 95% level were included.

the UCLP + b group 10 months after surgery. This implies that shape parameters of the upper dental arch in cUCLP patients approached the shape parameters in the patients with a less serious cleft type (UCLP + b).

3.2. Size changes

We used ANOVA to evaluate the possible individual or combined effects of the cleft type (cUCLP and UCLP + b patients) and cleft severity (mild, moderate, severe) on growth of the upper dental arch segments during the first year of life (Table 1). The results indicated significant effects of cleft type, cleft severity, and of interaction between cleft type versus cleft severity on the reduction of alveolar cleft width (1–7) and anterior basal angle (1–3 -7), and on the increase of the intertuberosity width (6–10) 10 months after surgery. There was also significant effect of cleft severity and cleft type on intercanine width (4–8). No other dimensions were significantly influenced by the cleft type, cleft severity, or their interaction.

Table 2 shows differences in the changes of maxillary dental arch dimensions during the first year of life between the cUCLP and UCLP + b groups. There were no significant differences in intermolar width (5–9), intercanine width (4–8) or palatal length (2–11). In comparison with the UCLP + b patients, the cUCLP patients (i.e. more serious cleft type) showed a greater change in the anterior limits of the upper dental arch segments during the first year of life: greater degree of reduction in the mean alveolar cleft width (1–7) and the anterior basal angle (∠1–3 – 7), this reduction was more pronounced with increasing cleft severity. On the other hand, the UCLP + b patients exhibited a more pronounced enlargement of the mean intertuberosity width (6–10), which became more distinct with decreasing cleft severity (Table 1).

The dimensions in our neonatal cheiloplasty group (intercanine and intertuberosity widths, palatal length) were compared with similar published data from a non-cleft group and an LOP group [22] (Fig. 3). This comparison was only descriptive and indicated that the upper dental arch in neonatal cheiloplasty groups (cUCLP and UCLP + b) showed growth trends depicted by the curve courses that were similar to the non-cleft group and to the LOP group. The exception was the

Table 1
Summarized Two-way ANOVA (F value) for cleft status and cleft severity and their interaction.

Variable difference	Cleft status	Cleft severity	Interaction
1–7	45.02***	77.2***	28.25***
8–10	1.64	2.40	1.38
5–9	3.46	3.76	3.05
4–8	4.84*	7.68**	2.94
4–6	0.56	0.34	0.63
6–10	12.08**	7.43**	4.41*
2–11	3.27	1.37	0.68
1-3-7	21.66***	38.39***	16.61***

*p ≤ 0.05.
**p ≤ 0.01.
***p ≤ 0.001.

Table 2
Differences in changes of linear (mm) and angular (°) measurements of maxillary dental arch during the first year between both cleft groups.

cleft type dimension	cUCLP	UCLP + b	p value
	x̄ ± SD	x̄ ± SD	
1–7	5.22 ± 3.44	1.99 ± 2.57	**
8–10	4.64 ± 2.61	3.50 ± 2.61	NS
5–9	3.05 ± 2.23	4.06 ± 2.48	NS
4–8	0.01 ± 2.71	1.42 ± 2.81	NS
4–6	3.67 ± 2.24	3.08 ± 4.41	NS
6–10	2.15 ± 1.71	4.71 ± 2.15	**
2–11	2.91 ± 2.25	1.46 ± 2.78	NS
1-3-7	10.73 ± 7.57	4.74 ± 5.21	**

*p ≤ 0.05.
**p ≤ 0.01.
***p ≤ 0.001.
NS (not statistically significant).

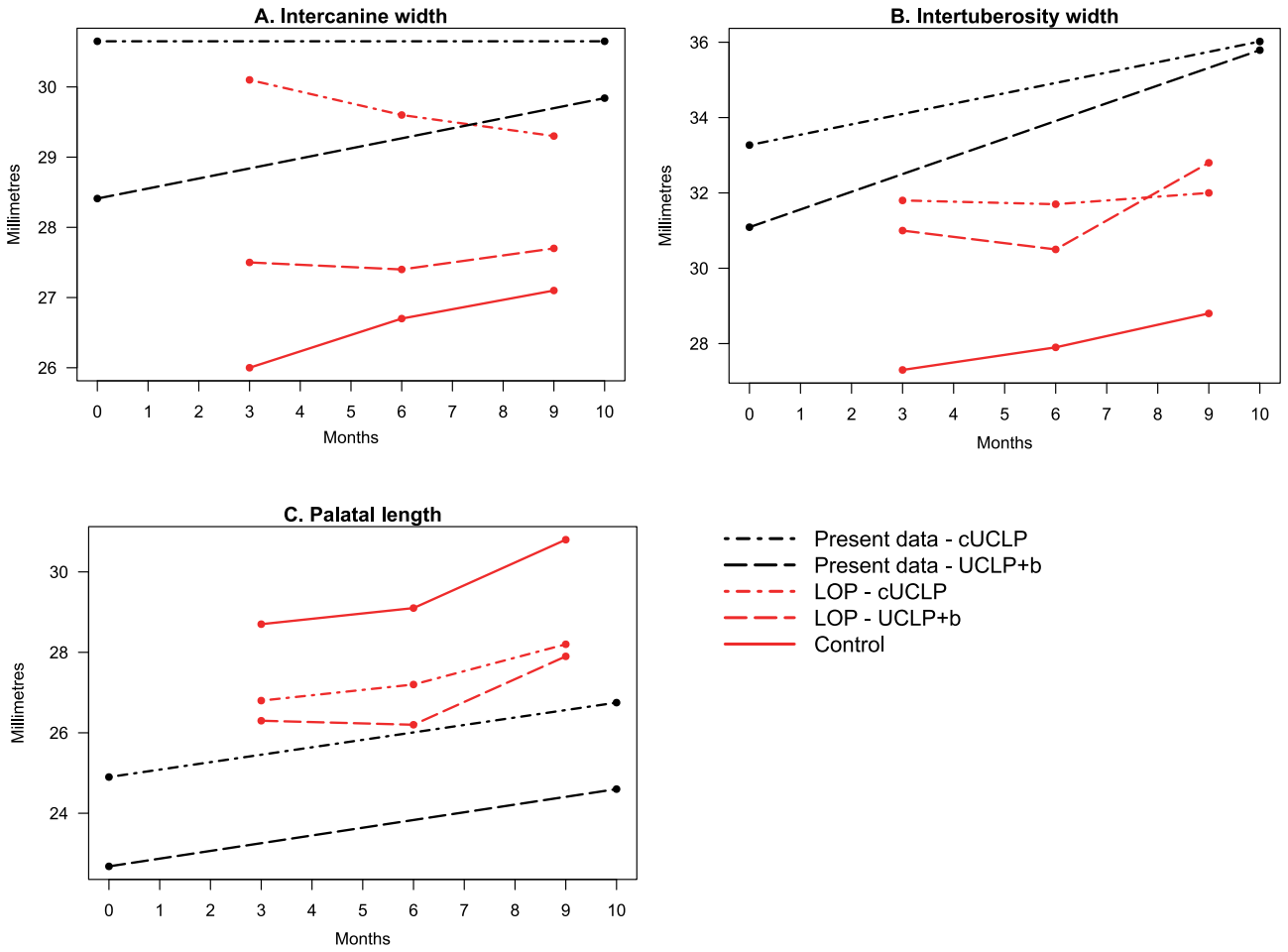

Fig. 3. Comparison of the growth of the upper dental arch in cleft and non-cleft groups. Three mean linear maxillary dental arch measurements (A–C) were taken at different ages (x axis) and demonstrate the corresponding size of the upper dental arch (y axis) in cUCLP, UCLP + b and control groups. Early neonatal cheiloplasty groups (present data) are compared with the published data on later operation protocol (LOP) or noncleft groups (control). A – Intercanine width; B – Intertuberosity width; C– Palatal length.

growth trend of the intercanine width in the cUCLP patients, where the LOP group showed the opposite trend to the neonatal group.

3.3. Segment growth visualization

Using pair analysis, we modelled the growth of the upper dental arch in the cUCLP and UCLP + b groups during the first year of life using colour-coded maps (Fig. 4). In the cUCLP patients (Fig. 4A–C), distinctive growth was observed in the anterior part of both segments, resulting in decreasing anterior cleft width. In addition, the posterior parts of both segments were growing, more noticeably on the noncleft side. In the UCLP + b patients (Fig. 4D–F), the most distinct growth concerned the posterior parts of the segments. Growth of the anterior part of the segments was the same as in the cUCLP patients.

4. Discussion

The aim of current study was to evaluate the growth of the upper dental arch in cUCLP and UCLP + b patients, to determine whether cheiloplasty has negative effect on growth of the upper dental arch and to statistically test the effects of the cleft type and severity on the growth of the upper dental arch.

Evaluation of the size and shape changes in the upper dental arch segments using 2-D and 3D methods showed apparent growth in the anterior and posterior parts of the split segments, in both cleft types.

4.1. Benefits of neonatal cheiloplasty

The early neonatal cheiloplasty has many benefits such as good aesthetic results of the lip scars, the appearance of the nose [10] and better child socialisation. In addition to above mentioned benefits, early neonatal cheiloplasty helps to deal with OME (otitis media effusion), which affects 92–97% of children with cleft palate in the first year of life. The high incidence of OME in cleft palate patients has largely been attributed to Eustachian tube (ET) dysfunction [15]. This dysfunction is primarily related to the inability of the TVP (tensor veli palatine) muscle to dilate the ET actively during swallowing. This appears to be the major factor responsible for the pathogenesis of OME (otitis media with effusion) in the population [24]. Contributory factors could also be failure of the Eustachian tube to close [25] or increased inclination to middle ear infection [26]. Early and active treatment results in maintaining normal hearing levels in the very critical years of language, speech, and cognitive development. It also prevents irreversible changes of the middle ear's structures in form of severe type retractions, or development of the chronic otitis with cholesteatoma [27]. The high frequency tympanometry and otoacustic emmissions (OAE) was performed in patients under general anesthesia before the early neonatal cheiloplasty and in the case of the presence of a secretion in mid ear cavity, otomicroscopy and evacuation of the fluid was performed.

4.2. Correlation between cleft type and severity

Several studies [18,28,29] have documented cleft severity as an

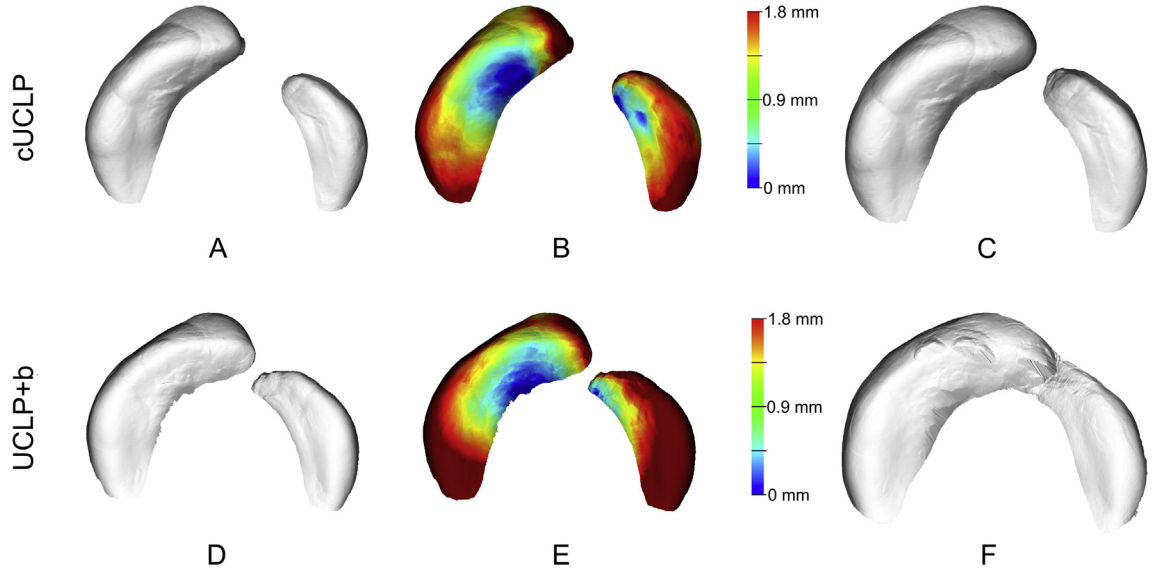

Fig. 4. Growth of the upper dental arch in the first year of life modelled by pair analysis. cUCLP patients (A–C), UCLP + b patients (D–F). A, C – Mean 3D model before early neonatal cheiloplasty. C, F - Mean 3D model at the age of 10 months. B, E − Growth visualization using mean distances of homologous vertices on neonatal and 10-month surfaces. The growth distances are visualized by colour-coding the mean mesh.

essential variable that might affect surgical and growth outcome. Kramer et al. [30] reported that alveolar cleft width, which is greater in cUCLP patients than in UCLP + b patients, decreased during development more in the cUCLP than in the UCLP + b patients. These findings were confirmed in our study. Furthermore, we found, that the parameters characterising the pathological maxillary protrusion – alveolar cleft width and anterior basal angle – were more pronounced with increasing cleft severity before cheiloplasty. A significant effect of cleft severity on the negative relationship between cleft size and palatal length was found in many studies [18,28,31], but our results showed that palatal length did not correlate with cleft severity.

4.3. Growth of the upper dental arch after cheiloplasty

Studies evaluating growth changes of the upper dental arch after later cheiloplasty (performed at age 3–6 months) have reported a decrease in intercanine width in cUCLP patients [6,22,32,33]. In both our groups (cUCLP, UCLP + b), we found a non-significant increase in intercanine width. The growth trend of the intercanine width in our patients was more similar to the physiological growth trend in the noncleft control groups [22,34]. An explanation could be that our patients were operated using a different surgical procedure—modified from the method of Tenisson – which brings extra material to the suture region and reduces lip tension [14].

The intertuberosity width and palatal length significantly increased in both groups during the monitored period, as in other studies [6,22,32,33]. Apparently, surgery performed at 3–6 months [22,33,35] and early neonatal cheiloplasty result in similar growth trends of intertuberosity width and palatal length.

4.4. Reduction of variability of the upper dental arch configuration

It is known that shape variability of the upper dental arch is higher in cleft patients than in the noncleft group [36]. PCA of the upper dental arch configuration in cUCLP patients (aged 0 and 1), together with that of UCLP + b patients of the same ages showed that shape variability of the upper dental arch in cUCLP patients at age 0 was much higher than in other groups, but it had also decreased more significantly by 10 months post-surgery. The method of approximating the variability in the cUCLP and UCLP + b groups suggests that the upper dental arch in patients with a more serious cleft type (cUCLP) tended to converge to a shape similar to that of patients with a less serious cleft type (UCLP + b). In our previous study [37] we observed similar results in cUCLP patients, where the initial variability decreased during 10 months following cheiloplasty.

4.5. Anterior growth of the upper dental arch segments

Huang et al. [6] have found growth in both the anterior and posterior parts of the upper dental arch after later cheiloplasty (3 months). Our data showed similar results after the early neonatal cheiloplasty. This indicates that neonatal lip closure did not prevent growth in the anterior part of the upper dental arch.

An occlusive effect of the reconstructed lip has been reported during formation of the upper dental arch [38]. We used pair analysis to visualise the growth of the segments following early neonatal cheiloplasty in both cleft groups (cUCLP, UCLP + b). These methods, together with 2-D measurements, showed increases of the width and length dimensions of the upper dental arch. This was accompanied by a reduction of the alveolar cleft width (1–7) and anterior basal angle (∠1–3 – 7). The contemporaneous increase of the width dimensions of the upper dental arch including the intercanine distance suggest that the reduction of the alveolar cleft and anterior basal angle were not caused by a narrowing of the upper dental arch. Instead they support the natural formative effect of the reconstructed lip on the actively growing anterior parts of split segments, which grew towards each other narrowing the cleft in the upper dental arch.

5. Conclusion

The lip suture did not prevent growth of the upper dental arch anteriorly, and it caused no narrowing of the upper dental arch. The results also demonstrated moderate differences in the upper dental arch growth after neonatal cheiloplasty between the children with UCLP and UCLP + b. The shape variability of the more serious cleft type (cUCLP), is considerably larger in neonatal period than in the less serious cleft type (UCLP + b), but after 10 months the shape variability in cUCLP patients decreased and approached the shape variability in UCLP + b patients.

Our data suggest that the reconstructed lip exerts a natural formative effect on the actively growing anterior parts of split segments, which grow towards each other thus narrowing the alveolar cleft in the

upper dental arch. The reduction of the alveolar cleft (gap) correlated with increasing cleft severity.

Conflicts of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Three-dimensional evaluation of facial morphology in pre-school cleft patients following neonatal cheiloplasty

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ABSTRACT

Purpose: To evaluate the facial morphology of pre-school patients with various types of orofacial cleft after neonatal cheiloplasty in pre-school aged children; and to compare facial variability and mean shape with age-corresponding healthy controls.
Materials and methods: The sample included 40 patients with unilateral cleft lip (CL), 22 patients with unilateral cleft lip and palate (UCLP), and 10 patients with bilateral cleft lip and palate (BCLP). Patients were divided into two age categories, with a mean age of 3 years and 4.5 years, respectively. The group of healthy age-matched controls contained 60 individuals. Three-dimensional virtual facial models were evaluated using geometric morphometry and multivariate statistics methods.
Results: Statistically significant differences were found between each of the cleft groups and the controls. Color-coded maps showed facial shape deviations, which were located mainly in the nasal area and philtrum in all groups examined, and also in the buccal region and the chin in patients with UCLP or BCLP. These differences became more apparent, but not significantly so, in the older age category.
Conclusion: Facial deviations typical of patients with clefts were observed in all of the patient groups examined. Although the analysis showed statistically significant differences in overall facial shape between patients and controls among all groups tested, the facial morphology in patients who have undergone only neonatal cheiloplasty (CL) is influenced to a small extent and may be considered satisfactory. More severe cleft types (UCLP, BCLP) together with palatoplasty, are reflected in more marked impairments in facial shape.

1. Introduction

Orofacial clefts are among the most common types of congenital structural malformations worldwide. The incidence varies from 1/500 to 1/2500 cases, depending on geographic location and ethnicity (Schutte and Murray, 1999; Vanderas, 1987). In persons of white ethnicity, the figure is between 1/600 and 1/700 (Murray, 2002; Tolarova and Cervenka, 1998; Vlastos et al., 2009).

During normal craniofacial growth, the oronasal components fuse together and form facial structures including the palate and lip (Weinberg, 1994). Any alteration during the process can disrupt or prevent the closure of components at the right time, and thus result in clefting. Consequently, the skeletal and tissue growth of the whole area is affected negatively (Diah et al., 2007; Weinberg, 1994).

Primary surgical closure of the soft tissue of the lip and nose (i.e., primary cheiloplasty) is the first and probably the most discussed step in the treatment of patients with a cleft lip or cleft lip and palate (Habel et al., 1996; Schutte and Murray, 1999). The main aims of primary surgical treatment are the restoration of orofacial tissue, which enables normal functioning such as feeding, and reconstruction of facial appearance (Borsky et al., 2012). If the defect is

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more severe or is combined with cleft palate, other surgeries usually follow (Habel et al., 1996).

The worldwide accepted timing range for performing primary cheiloplasty is between 2 and 6 months of age; it is usually done at 3 months of age (Harris et al., 2010; Mcheik et al., 2006). In the past 20 years, the idea of performing surgery at an alternative time, early in the neonatal period (i.e., within approximately 10 days of birth) has emerged. It has been suggested that a successful surgery performed earlier in life can minimize the negative impact (especially psychosocial) of the cleft (Goodacre et al., 2004).

The advantages and disadvantages of such early surgery are often discussed in the literature. The original concerns were related especially to the safety of general anesthesia at such an early age. However, no difference was found in the probability of cardiac arrest or occurrence of perioperative complications between neonates and 3-month-old children (Bhananker et al., 2007; Murat et al., 2004).

Moreover, it has been suggested that healing and scar formation are different shortly after birth than at later ages (Li et al., 2014). During intrauterine development, instead of scarring, fetal fibroblasts deposit matrix in a pattern that resembles normal skin (Adzick and Lorenz, 1994). This process, called scarless healing, can persist even after birth for a short period of time. Thus, an earlier timing of surgery can be beneficial for healing and also for the overall appearance of the cleft area (Adzick and Longaker, 1992; Borsky et al., 2012). The aesthetic results of the surgery are as good as in patients undergoing delayed surgery. This implies that surgeons are equally able to achieve a favorable outcome regardless of the timing of the repair (Goodacre et al., 2004).

Psychosocial advantages speak in favor of neonatal timing as well. Parents prefer to bring their neonate home with no visible deformity. Immediate closure of the cleft also simplifies feeding of the infant and thus, later, it can even have a positive impact on weight gain and normal growth (Borsky et al., 2012).

Overall, the current literature mostly agrees on the benefits of neonatally performed cheiloplasty (Akin et al., 1991; Goodacre et al., 2004; Harris et al., 2010; Borsky et al., 2012; Petráčková et al., 2015). Despite this, not much has been written about growth and development of the face itself after the procedure and in later years. The initial results suggest that the data acquired on maxillary growth after neonatal surgery (Borsky et al., 2012) are consistent with findings obtained on a group of patients operated on at an average age of 3.2 months (Huang et al., 2002). According to Akin (Akin et al., 1991), neonatal surgery has a significantly positive occlusive effect on the alveolar arch, which does not need further surgical correction.

This study aimed to evaluate facial morphology in various preschool age patients with orofacial cleft who underwent neonatal cheiloplasty, in comparison with healthy controls of corresponding ages.

2. Materials and methods

This study was approved by the Ethics Committee of The Institutional Review Board of Charles University, Faculty of Science. The study was performed in accordance with the guidelines of the Declaration of Helsinki. Declaration and informed consent forms were signed by parents/legal representatives of the children before any intervention.

The participants in this study included patients with unilateral cleft lip (CL), unilateral cleft lip and palate (UCLP), and bilateral cleft lip and palate (BCLP). Individuals with atypical clefts or associated syndromes were not included. All patients underwent surgery at the Faculty Hospital Motol, Prague, Czech Republic, by the same surgeon. Primary cheiloplasty was performed using the same modified Tennison method within the first 8 days (or, exceptionally, 14 days) of life. Palatoplasty in the UCLP and BCLP groups was performed at a mean age of 10.21 months using the Furlow technique. The cleft patients studied consisted of two separate age categories, a younger category with a mean age of 3 years (2.5–3.7 years) and an older category with a mean age of 4.5 years (4.0–5.0 years); both categories contained subgroups with each of the three cleft types. The younger age category consisted of 42 patients (26 CL, 12 UCLP, 4 BCLP) and the older age category 30 patients (14 CL, 10 UCLP, 6 BCLP).

A control group of healthy children, from preschools in Letná and Hrabákova in Prague, were in the same age range as the patient group; the younger category comprised 22 individuals, the older 38 individuals.

Methods of geometric morphometry applied to three-dimensional (3D) facial scans allowed us to evaluate the facial surface in its entirety and to assess even minor changes precisely.

For the analysis, 3D facial models were used. Images were acquired by a noninvasive optical technique, using a high-resolution Vectra 3D scanner (Canfield Scientific, Inc., Fairfield, NJ, USA). During capture, each participant was seated in front of the scanner with the head in a natural position; the patient was asked to make a neutral facial expression. The final 3D facial model was generated using the associated software Mirror PhotoTools (Canfield Scientific, Inc.). Afterwards, each model was imported into the software RapidForm 2006 (INUS Technology Inc., Seoul, Korea) for further processing, which involved manual trimming of unwanted data or noise, filling holes in the model, and decimation.

Before statistical processing, vertex homology had to be enforced in the entire sample of surfaces. To that end, we used CPD-DCA (Dupej et al., n.d.), a modification of the original dense correspondence analysis (DCA) algorithm by Hutton et al. (2001). In contrast to DCA, which relies on landmark-fitted spatial deformations, CPD-DCA uses an automatic nonrigid registration algorithm coherent point drift (CPD) to find corresponding vertices, which results in more accurate correspondences outside the convex hull of the landmarks.

The processing started with rigid registration of the surfaces. Nine landmarks (exoR = right exocanthion; exoL = left exocanthion; enR = right endocanthion; enL = left endocanthion; N = nasion; Pn = pronasale; chR = right cheilion; chL = left cheilion; Pg = pogonion) were manually placed on every model, according to Hutton et al. (2001). Generalized Procrustes analysis (GPA) was performed on these landmarks and the resulting transformations were used to rigidly align the entire meshes. Next, a template mesh, called a base, was arbitrarily selected from the sample, as reported by Hutton et al. (2001). As long as the mesh had an even coverage of vertices, its choice had negligible bearing on the subsequent statistics. Then, the base was registered to each non-base mesh (called floating) with an automatic nonrigid algorithm. After registration, the closest points to the deformed base were found on the floating mesh, and these were considered homologous to the base's vertices. Because of this assumed homology, these vertices are dubbed quasi-landmarks. Poor correspondences were detected by ascertaining triangle compaction, and such quasi-landmarks were removed from further processing.

Finally, principal components analysis (PCA) was performed on the vertex coordinate matrix to reduce data dimensionality. Quasi-landmarks that were improperly matched were removed from the PCA and therefore did not introduce any unwanted variability. For purposes of visualization, these quasi-landmarks were imputed with a thin plate spline-based approach (Dupej et al., n.d.). This entire process was performed using the software suite Morphome3cs (http://www.morphome3cs.com/).

Shape variability was analyzed using PCA. Scatter plots with 95% confidence ellipses were plotted to visualize shape variability. PCA was calculated on shape variables, that is, size was normalized to unity in each subject.

Using PCA scatter plots, we observed the differences in variability between the group of patients as a whole and the group of controls as a whole, then between separate age categories, and finally among all cleft types and controls.

To assess the statistical significance of differences in shape among the separate groups, the Hotteling T-square test was performed on the PCA scores. A broken-stick criterion was used to determine the number of significant components included in the analysis (Peres-Neto et al., 2005). All analyses were performed in Morphome3cs.

To observe differences in facial shape between subgroups in the anteroposterior direction, we used tools available within Morphome3cs. Average faces for each group were constructed (Fig. 1). First, color-coded distance maps were used to visualize and to quantify shape differences between average shells. Generally, the more protrusive (anterior) placed parts of the shell are coded in red, the more deeply (posterior) situated parts are in blue, and parts with no difference are marked in green.

Using the shell distance significance tool in Morphome3cs, we were able to visualize statistically significant differences in shape between selected subgroups. This tool operates by calculating two-sample t-tests on shell distances from the grand mean surface over two groups of individuals. The corresponding p-values were visualized on the surfaces; areas with significant differences were coded in shades of blue, depending on the p-value.

Finally, to test the differences in intercanthal width, two-way analysis of variance and the Tukey honest significant difference (HSD) test were performed.

3. Results

We obtained an initial insight into the variability of shape in the cleft and control groups through scatter plots of the principal component scores. The broken-stick method indicated that the first 7 principal components (PCs) should be kept for statistical processing. A plot of scores in PCs 1 and 3 shows substantial overlap (Fig. 2A). We found that the most apparent separation of the groups could be observed between PCs 6 and 7 (Fig. 2B). It would follow that, as the PCs progressively decrease in the amount of variability explained, the differences among the groups are likely to be of a localized nature, as opposed to the pronounced variation in overall shape that would be captured in PCs with lower indices. Furthermore, the cleft groups exhibited a greater variability in the PC scores (Fig. 2).

Next, with Hotelling T2 tests on PC scores, we found that, in each cleft or control group, the shape means did not differ significantly between age categories. We therefore combined the data points from the 3- and 4-year-old subsamples. In Fig. 2, the groups are shown without regard to age.

Further testing of cleft group means against the control, with the Hotelling T2 test, revealed statistically significant differences in all of the cases tested ($p < 0.001$). Even in the case of the least severe cleft type (CL), the differences in corresponding PCA scores were significant.

After having established the presence of shape differences in specific groups of specimens using PCA scores, we inspected the differences in shape calculated per-vertex in Morphome3cs to pinpoint the areas on the surfaces that cause these results. The mean facial surface for each control/cleft type is presented in Fig. 1.

Fig. 3 shows color-coded maps for all group comparisons. First, we checked the influence of age on the facial shape within cleft/control groups (Fig. 4). We observed that those differences mostly concern the forehead (control, CL, BCLP) and the buccal region (CL). Interestingly, the facial shape appears not to undergo significant changes in the areas that we expect to be affected by the cleft, such as the nose or philtrum.

Next, we assessed the visualization of differences between controls and patients with clefts (Fig. 3). We noted that the patients with CL (Fig. 3A,D) had more prominent tissue on the cleft side of the upper lip, due to the postoperative scar. Also, the nostril on the

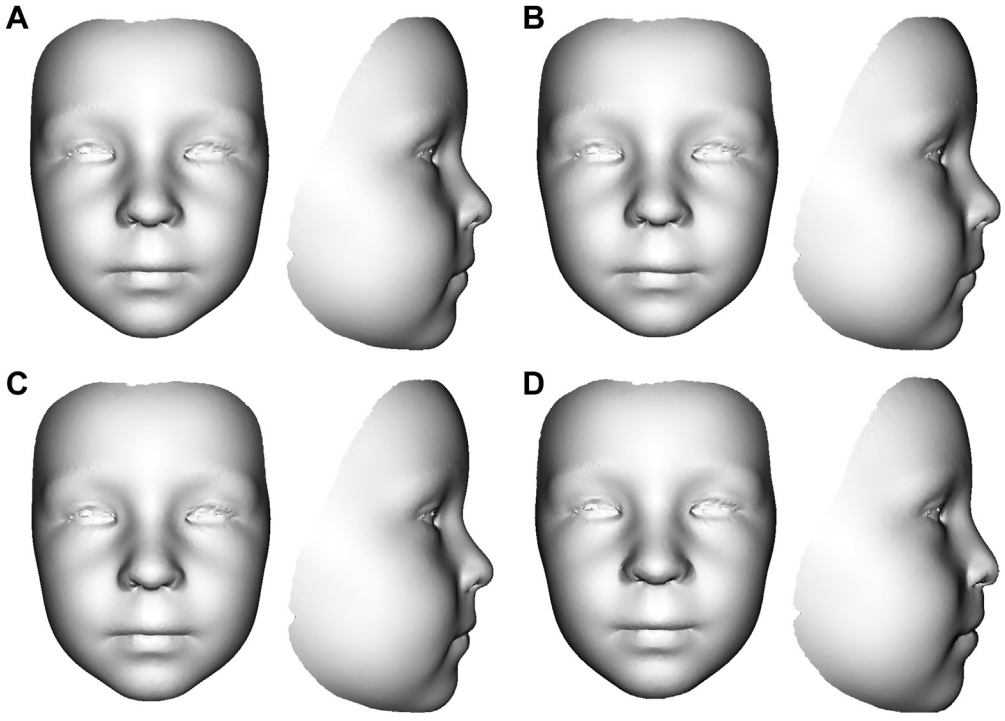

Fig. 1. Average face shape regardless of age of (A) controls, (B) CL group, (C) UCLP group, and (D) BCLP group.

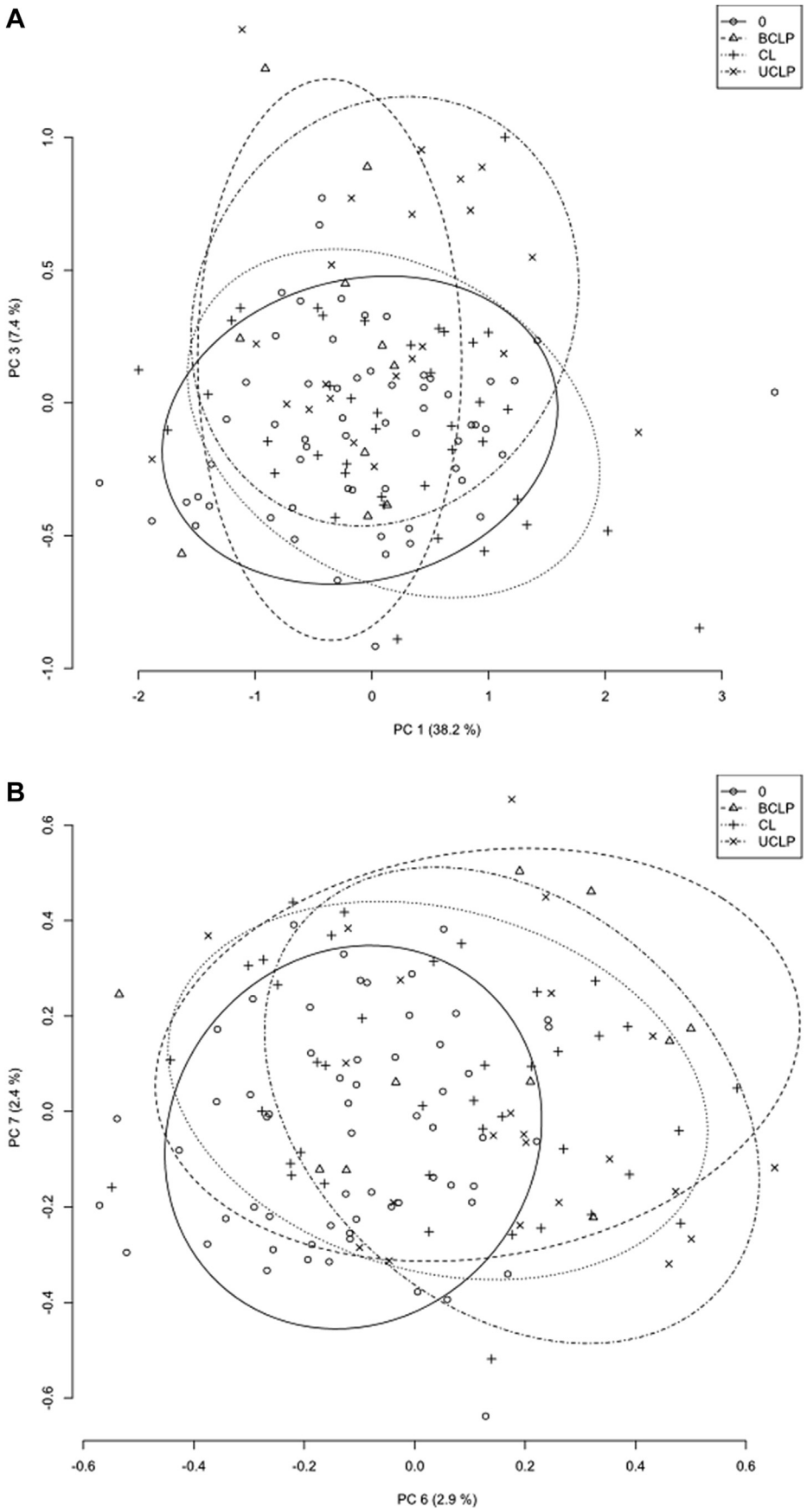

Fig. 2. Shape variability of cleft and control groups described by (A) PC1 and PC2, representing 40.7% and 19.3% of total variability, and (B) PC6 and PC7, representing 3.0% and 2.2% of total variability. Confidence ellipses for groups at the 85% level were included.

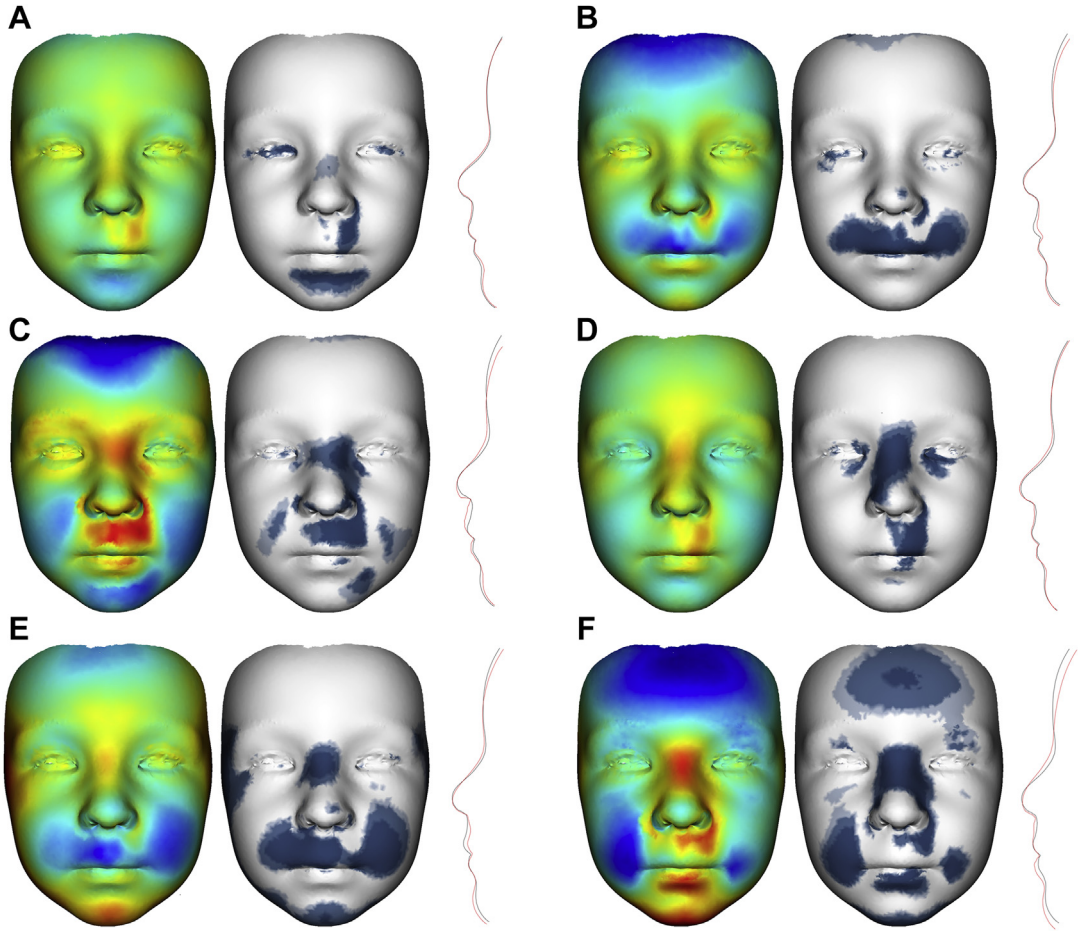

Fig. 3. Color-coded maps, shell distance significance maps and profile views (black = cleft group; red = controls) of the control face and (A) CL average face, (B) UCLP average face, (C) BCLP average face, mean age 3 years; (D) CL average face, (E) UCLP average face, and (F) BCLP average face, mean age 4.5 years.

corrected side was somewhat wider. One could also observe a flatter and less concave nasal root and a slightly less prominent chin, when compared with the control group of appropriate age. Albeit nonsignificant, the nasal tip also appeared less prominent than in the controls. The observed differences were less pronounced in the younger age category.

Unlike the CL group, there was a marked deviation of shape in UCLP patients, when compared with controls, in the area of the upper jaw (Fig. 3B,E). Whereas the upper part of the cleft area was on the same level as the upper jaw tissue in controls, the surrounding parts were situated relatively deeply in patients with UCLP. The tissue insufficiency extended to the buccal region, especially on the cleft side; this was more significant in the older group. However, there was more protrusion of the mental region in older patients with UCLP. The areas of the nasal root, nasal bridge, and nasal tip and the asymmetry of the alar base with the wider repaired nostril followed the same pattern as in the CL group. In the older category, the area of the nasal root was less concave than in controls and the nasal tip was less prominent, in this group, which was significant.

The differences between patients with clefts and the control group were most marked in the BCLP group (Fig. 3C,F). Flattening of the nasal root area was observable in both age categories, as was widening of the nasal bridge. The alar base was markedly wider on both sides. The area of the premaxilla is in significant protrusion in BCLP. Other protrusions are to be found in the lower lip, which was more pronounced in the older group. Buccal areas were flattened and deepened; concurrently, the forehead was less protruding, especially near the midline. In the younger category, the orbital region was more prominent (nonsignificantly) and, in the older category, protrusion of the chin and lower lip were apparent.

Finally, we tested the differences in intercanthal width among cleft types and age groups. This was done to learn whether the intercanthal distance changes with the flattening of the nasal root. Analysis of variance did not confirm the influence of age ($p = 0.769$) or cleft category ($p = 0.165$). The post hoc test indicated that there was no difference in intercanthal width between any combination of age and cleft type, with the exception of 3-year-old patients with UCLP when compared with 3-year-old controls ($p = 0.032$). In the CL and BCLP groups, that dimension was on average slightly greater, although the difference was not confirmed with the Tukey HSD test.

4. Discussion

Although currently there is no surgical method for cleft lip repair without at least minor negative consequences on facial growth, the result of surgery can differ depending on the protocol used and on various factors such as the timing of the procedure (Shi and Losee, 2015). However, typical deviations occur later in development as a result of further growth of the cranium and face, and are mostly observable some years after surgery. By then, it is usually not possible to distinguish the effect of primary surgery from the effect of other surgeries, such as palatoplasty, which the patient has undergone. Primary cheiloplasty is, however, the most important factor causing growth disturbances, generally in the maxillary region (Capelozza et al., 1996). Evaluation of the

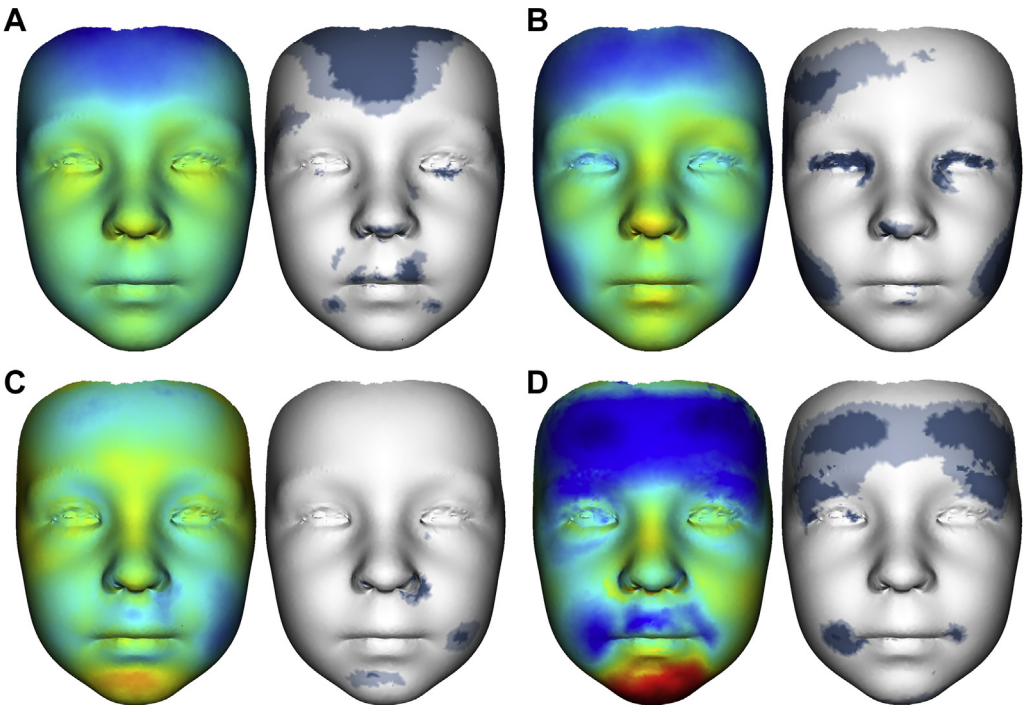

Fig. 4. Color-coded maps and shell distance significance maps describing facial shape differences between age categories for (A) controls, (B) CL group, (C) UCLP group, and (D) BCLP group.

differences in facial morphology in patients with different types of cleft may help us to distinguish the influence of primary lip repair and that of later surgeries.

Our study aims were to assess the development of facial shape after neonatal cheiloplasty in patients of pre-school age with different cleft types, and to compare these findings with the facial morphology of healthy control groups of corresponding ages. Given that three cleft types were included in our study, we were able to distinguish the influence of neonatal cheiloplasty only (CL group) and the influence of neonatal cheiloplasty combined with later palatoplasty in patients with more severe clefts (UCLP, BCLP). Our research also aimed to collect a complex dataset suitable for possible comparison with findings from patients who undergo cheiloplasty at later ages.

According to the PCA results, the variability in facial shape of all tested cleft groups and controls overlapped substantially. Although the UCLP and BCLP groups, with the most severe cleft types, were visually discriminated from the others by PC3, the trend was related to only a few individuals. Mostly, the groups in PC1 and PC3 space showed similar distributions. In the space of PC6 and PC7, all cleft types were partially distinguished from the controls. Our results thus differ from the findings of Singh et al., who described the variability of patients with UCLP as following a distribution similar to that in a healthy control group, even though the shape variation was larger in their patients (Singh et al., 2007). These differences could have been caused by the different ages of the patients evaluated or by the fact that, in our sample, the patients with clefts were, in terms of morphology, more similar to controls. According to Bejdová et al. and Rusková et al., who studied the variability of palatal shape in BCLP and UCLP patients and controls, PCA showed that variability of clefted and nonclefted palatal shapes overlapped only to a very small extent, and the variability in patients was much higher than that in controls (Bejdova et al., 2012; Rusková et al., 2014). In contrast to our study on facial shape, we can conclude that the palatal shape in patients with BCLP and UCLP in both of these studies was more negatively affected than the face.

As described previously, the degree of deviation varies depending on the severity of the cleft (Honda et al., 1995; Smahel, 1984). According to Bugaighis et al., the most severely affected groups, in terms of morphology, are those with defects involving the lip, alveolus, and palate together (UCLP and BCLP) (Bugaighis et al., 2010). That is in concordance with our results on facial shape variability.

Using color-coded maps, we could observe evident shape differences in comparison with controls in every facial area, even where the differences were present but not statistically significant. The observed deviations mostly correspond with typical changes, as frequently described (Capelozza et al., 1996; Ferrario et al., 2003; Smahel and Brejcha, 1983).

According to Duffy et al., the growth retardant effect of CLP surgeries can be manifested transversely as high as the orbital level and the forehead (Duffy et al., 2000). Consistently, we observed differences in the forehead area in the UCLP and BCLP groups. The forehead was less prominent than in controls, as described by Duffy et al. and Djordjevic et al. Together with other typical traits, this can contribute to a typically flattened profile (Djordjevic et al., 2012; Duffy et al., 2000). Although the deviation was observable, the only group in which the differences in this region reached statistical significance was the older category of patients with BCLP. There were no differences in the CL groups at all.

Evaluation of the intercanthal width across groups showed that significantly greater intercanthal width was found only in the younger UCLP group in comparison with controls. In the younger CL and BCLP groups, this dimension was nonsignificantly greater. Aduss et al. (1971) found a greater increase in interorbital distance in patients with cleft lip and in those with cleft lip and palate (in most cases, the increase did not exceed 1 standard deviation) than in patients with only cleft palate. This finding suggested that the differences in interorbital distance, although mostly insignificant, may reflect abnormal development of the nasofrontal process, as previously mentioned. A greater nasal bridge width, found even in the CL patients in our study, supported this theory.

Nasal deformities have always been a fundamental problem in the treatment of patients with clefts. Even in the least severe (CL) group, we observed significant widening of the nostril on the clefted side. In patients with UCLP as well as those with BCLP, the alar width is most markedly widened on both sides. These are typical patterns that have been described repeatedly (Ayoub et al., 2011; Bugaighis et al., 2014, 2010; Duffy et al., 2000). During the primary surgery, it is not possible to restore the loss of the medial insertion points of the facial muscles, which may explain these findings (Zreaqat et al., 2012). In addition, the area of the nasal root also differed in all groups. In the patient groups, it was less concave than in the controls, and thus made the facial profile look flatter. The trait was least marked in younger patients with CL and UCLP and most marked in the BCLP groups. Flattening of the profile in patients with cleft is a typical trait that has repeatedly been described in the literature (Capelozza et al., 1996; Ferrario et al., 2003).

The maxillary region and the whole mid-facial area are usually considered to be most problematic in patients with cleft (Capelozza et al., 1996; Diah et al., 2007). In patients with BCLP, the deviations are even more severe, owing to premaxilla displacement (Honda et al., 1995), which is in concordance with our findings. Even years after surgery, we could observe significant protrusion of the philtrum area in the BCLP group. In contrast, Bugaighis et al. found that, later in development, within the age category 8–12 years, the upper lip and mid-facial area in the BCLP group seemed flatter and more retruded (Bugaighis et al., 2014). In the UCLP group, the maxillary area (with the exception of a protruding scar) was significantly deepened as a result of the growth deficiency. The deepening overlapped with the buccal region, and the cheek on the cleft side was more retruded, as has been reported by Djordjevic et al. and Bugaighis et al. (Bugaighis et al., 2010; Djordjevic et al., 2012). Maxillary and buccal retrusion was also found in the BCLP group, where both cheeks were deepened approximately equally, as was found also by Duffy et al. (Duffy et al., 2000). On the other hand, in the CL group, the only difference in the maxillary region was caused by an anteriorly pronounced scar. There was no buccal retrusion. This finding indicated that neonatal cheiloplasty probably has no negative influence on maxillary development. The insufficient growth of the midface in patients with UCLP and BCLP is caused by a combination of the severity of the craniofacial defect, which in this case affects also the hard palate and the surgeries.

Differences in the area of the chin have also been found, in concordance with findings that even the area of the mandible can be affected in patients with cleft (Smahel, 1984; Smahel and Brejcha, 1983); however, in our study, this had no strong pattern. In older categories of patients with UCLP and BCLP, the chin was more prominent. On the contrary, in both age categories of the CL group, the upper part of the chin, under the lower lip, was less prominent when compared with those of controls.

5. Conclusion

This study indicates that, in terms of facial development, neonatal cheiloplasty can be performed as an adequate method, comparable to surgery performed later in life. However, neonatal cleft lip repair can still be a cause of minor craniofacial growth impairment. Generally, we have reported shape deviations that have been repeatedly described as typical of patients with cleft. In the group of patients with CL, who underwent only a single surgical procedure (neonatal cheiloplasty), the differences in comparison to controls were minor and observable only in the cleft area itself, in the nostril on the cleft side, at the nasal bridge and on the chin. The area of the maxilla and midface, even though it is usually the most problematic in cleft patients, was not affected, with the exception of the surgical scar. In patients with UCLP or BCLP, we observed more severe growth impairments. This indicates that the defect of the palate, together with palatal surgery may have a negative influence on facial growth in patients with cleft. However, even though the overall facial shape differentiated all cleft groups from the control group significantly, the variability within the cleft and noncleft groups still allowed substantial overlap, even in the case of the UCLP and BCLP groups. We have also found that the deviations that were present in patients at a mean age of 3 years were not significantly more pronounced in the older age category, at approximately 4.5 years, which seems promising for later development.

Acknowledgment

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Three-dimensional assessment of facial asymmetry in preschool patients with orofacial clefts after neonatal cheiloplasty

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ABSTRACT

Objectives: To evaluate facial asymmetry changes in pre-school patients with orofacial clefts after neonatal cheiloplasty and to compare facial asymmetry with age-matched healthy controls.
Methods and materials: The sample consisted of patients with unilateral cleft lip (UCL), unilateral cleft lip and palate (UCLP), and bilateral cleft lip and palate (BCLP). The patients were divided in two age groups with a mean age of 3 years (n = 51) and 4.5 years (n = 45), respectively, and 78 age-matched individuals as controls. Three-dimensional (3D) facial scans were analyzed using geometric morphometry and multivariate statistics.
Results: Geometric morphometry showed positive deviations from perfect symmetry on the right side of the forehead in the intervention groups and the controls. The UCL groups showed the greatest asymmetric nasolabial area on the cleft-side labia and the contralateral nasal tip. The UCLP group showed, moreover, asymmetry in buccal region due to typical maxillar hypoplasia, which was accentuated in the older group. The BCLP groups showed slightly similar but greater asymmetry than the control groups, except for the philtrum region.
Conclusions: Asymmetry of each of the cleft groups significantly differed from the controls. Except for the buccal region in the UCLP and BCLP groups, asymmetry did not significantly increase with age.

1. Introduction

Facial symmetry refers to a state of balance, where the size, form, and arrangement of facial tissues and structures on the opposite sides of the median sagittal plane correspond. Thus, the right and left sides in the craniofacial complex, comprising identical structures, must grow and develop equally to reach symmetry [1]. Nonetheless, a mild degree of asymmetry is a common biological characteristic in healthy individuals [2].

The degree of asymmetry considered to be reasonable often varies between 2 and 4 mm [3]. There are no existing objective standards for establishing abnormality [4] and it is often determined by the clinician's perception of balance and the patient's perception of imbalance [5].

The etiology of facial asymmetry for many cases is still unknown but it can be attributed to genetic and environmental factors or a combination of both [6,7]. Hence, the etiology of asymmetry can be grouped into three main categories, (A) congenital, originating prenatally; (B) developmental, arising during growth with inconspicuous etiology; and (C) acquired, resulting from injury or disease [8].

The theoretical basis for congenital asymmetry is that the lower and midface develop from the medial and lateral nasal processes as well as maxillary and mandibular processes, and despite innate synchronization, these structures might indicate failure of development or maturation of such embryonic processes [9]. The changes associated with facial asymmetry comprise facial clefts, hemifacial microssomia, congenital muscular torticollis, unilateral coronal craniosynostosis, positional plagiocephaly and others [8].

As yet, there is no reasonable explanation for the causative mechanism of lateral guidance of the face but it might be related to the imbalanced development of neural crest cells. It has been speculated that neural crest cell migration happens earlier on the right side and tends to be delayed on the left side [9,10]. It could be associated with preferential laterality for some anomalies, such as cleft lip, which occur

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more commonly on the left side.

Facial asymmetry is one of the most common features in cleft lip or cleft lip and palate patients [11]. The UCL nasal deformity is dominated by the asymmetry of the soft tissue in the lip and nose area, as well as in the underlying skeleton [12]. However, there was no statistically significant difference between the amount of facial asymmetry in children with repaired isolated cleft palate and their healthy peers [13].

Treatment of cleft lip and palate patients is focused on the soft tissues of the lip and nose, and the hard tissues of the maxilla and dental abnormalities [14].

Neonatal cheiloplasty performed in the first week of life solves some of the problems connected with cleft lip such as feeding problems, and leads to positive psychosocial outcomes for the whole family, enhanced wound healing and excellent aesthetic results [15]. However our previous results revealed that it is still a cause of minor craniofacial growth impairment. The differences in patients with cleft lip only were least and observable only in the cleft area itself [16].

This study aimed at illustrating and evaluating facial asymmetry in pre-school patients with various orofacial clefts who underwent neonatal cheiloplasty. To find out if there are any developmental trends in asymmetry two age groups of patients were selected. The visualization and 3D analysis of facial asymmetry in healthy children was carried out to detect any similarities in asymmetry with cleft patients.

2. Participants and methods

2.1. Participants

The intervention group consisted of 96 patients with unilateral cleft lip (UCL), unilateral cleft lip and palate (UCLP) and bilateral cleft lip and palate (BCLP). Individuals with associated syndromes were excluded from the study. All the patients were Caucasian and underwent surgery at the Faculty Hospital Motol, Prague, Czech Republic, by the same surgeon. Primary cheiloplasty in all the patients was performed using the modified Tennison's method within the first 10 days of life (exceptionally 14 days). The UCLP and BCLP groups underwent palatoplasty, which was performed at a mean age of 10.3 months using Furlow's technique by the same surgeon. The intervention group was comprised of two separate age groups and both groups contained subgroups with each of the three cleft types. The younger category with a mean age of 3 years (2.5–3.7 yrs) consisted of 51 patients (31 UCL, right-8, left-23; 15 UCLP right-3, left-12; 5 BCLP). The older category with a mean age of 4.5 years (4.0–5.0 yrs) consisted of 45 patients (21 UCL, right-8, left-13; 15 UCLP, right-9, left-6; 6 BCLP).

The control group consisted of age-matched healthy children attending preschools in Letná, Hrabákova, Kolovraty and Vozová in Prague. The younger subgroup in the control group was comprised of 40 individuals and the older subgroup was comprised of 38 individuals. All the children in the control group had harmonious balanced faces and no craniofacial abnormalities.

2.2. Methods

A facial scan was obtained from each subject using a non-invasive optical scanner Vectra 3D (Canfield Scientific Inc., Fairfield, NJ, USA) and 3dMDface System (3dMD Limited, Brentford, London, UK). Surface models were built automatically using the bundled software. Next, each model was processed in RapidForm 2006 (INUS Technology Inc., Seoul, South Korea). The processing involved manual trimming with removal of the ears, neck and hair, closure of any holes and simplification to roughly 30k triangles. Finally, scans with a unilateral cleft on the right side were reflected about a plane to keep all clefts on the left side.

Before any statistical processing of the surfaces, vertex homology had to be enforced. This was done using CPD-DCA [17], which is an extension of the original DCA that uses an automatic nonrigid registration algorithm. Nine landmarks were placed on each model in standard locations (exoR = right exocanthion; exoL = left exocanthion; enR = right endocanthion; enL = left endocanthion; N = nasion; Pn = pronasale; chR = right cheilion; chL = left cheilion; Pg = pogonion). These landmarks were used for rigid prealignment of the facial surfaces by means of Generalized Procrustes Analysis (GPA). Vertex homology was created by resampling all surfaces based on one arbitrarily chosen surface from the sample called the *base mesh*. Automatic nonrigid registration and projection of the base mesh to each surface was used to transfer the topology of the base mesh to all other meshes. The resulting vertices can be considered homologous across the data set and are subject to the same methods as ordinary landmarks; they are therefore referred to as *quasi-landmarks*. Finally, the surfaces were rigidly aligned to a mean surface using GPA.

Detailed analysis of asymmetry was evaluated using special workflow in Morphome3cs software (www.morhome3cs.com), whose outputs are both color-coded maps and shell distance significance maps. From the *correspondence meshes*, *symmetric meshes* were created as follows. Each correspondence mesh was reflected about an arbitrary plane and resampled to the topology of its non-reflected counterpart with the same method that was used in the construction of correspondence meshes. Rigid alignment of these two surfaces with GPA also produced a mean surface, which was the sought symmetric mesh. Subtracting the symmetric quasi-landmarks from those of the correspondence meshes yielded the individual asymmetry (IA). For visualization, signed IA has been calculated. Sign of IA in each vertex has been determined based on the position of the correspondence vertex relative to the symmetrized vertex, with respect to local surface normal. Positive values were assigned if the correspondence vertex was in front of the symmetrized vertex; negative values if the converse was true.

The color-coded maps are interpreted in the following way: red areas that are in the front of the corresponding mirrored counterpart, suggest that they may be larger than the corresponding paired counterpart (= positive values of asymmetry), while blue areas are smaller and located behind the aligned mirrored counterpart (= negative values of asymmetry) [18]. Shell distance significance maps were used to show where the asymmetry was statistically significant. The corresponding p-values were coded in shades of blue.

In addition, asymmetry of the forehead in patients with left and right side unilateral clefts, which were unlikely to be associated with the oral defect, were separately analyzed for evaluation and illustration.

3. Results

Using scatter plots of principal components analysis, we visualized variability of asymmetry in the cleft and control groups. First, we observed that the cleft groups exhibited a greater variability in the principal components (PCs) scores than the controls. The first 6 PCs have been kept for statistical processing according to the broken-stick method criterion. The most apparent separation of the groups were observed from PCs 3 and 5 (Fig. 1).

Both the parametric and permutation version of Hotelling's T2 tests on PC scores revealed that in each cleft or control group, the degree of asymmetry did not differ significantly between age groups. This could not be confirmed between BCLP groups alone due to the small sample in the three-year-old group. Although there were no statistically significant differences between age groups in overall facial asymmetry, we decided to visualize age groups separately because of the possible presence of local differences.

Further testing was focused on cleft groups in comparison with the controls. The parametric and permutation version of Hotelling's T2 test detected statistically significant differences in all the cases tested; ($p < 0.01$) in the BCLP group, and ($p < 0.001$) in the UCL and the UCLP groups.

After determining the presence of the differences in asymmetry in specific groups of probands using PCA scores, we visualized the differences in asymmetry using color-coded maps and calculated per-

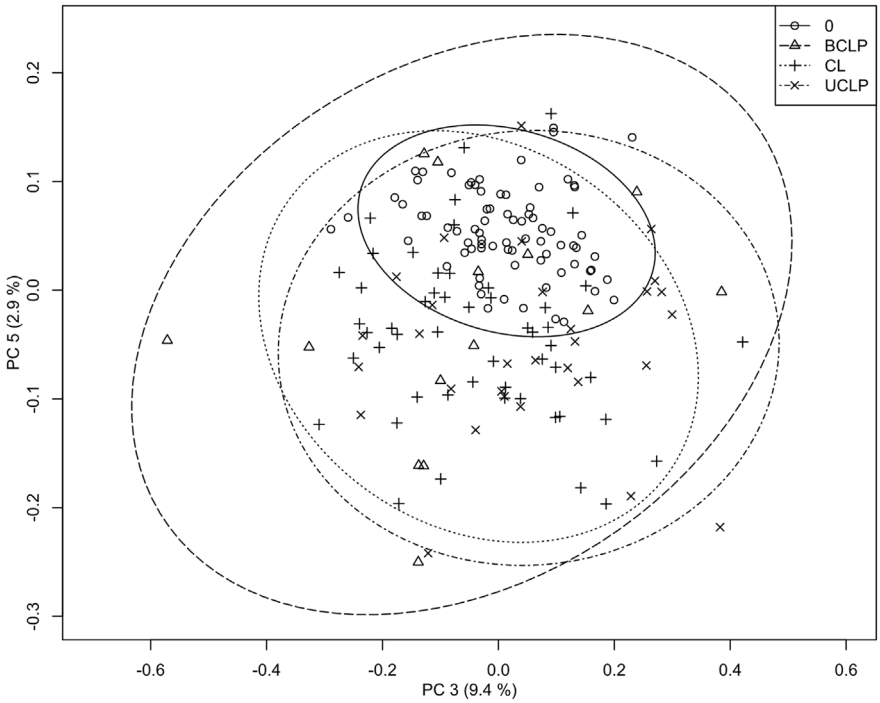

Fig. 1. Variability of facial asymmetry of cleft and control groups described by PC3 and PC5, representing 9.4% and 2.9% of total variability. Confidence ellipses for groups at the 95% level were included.

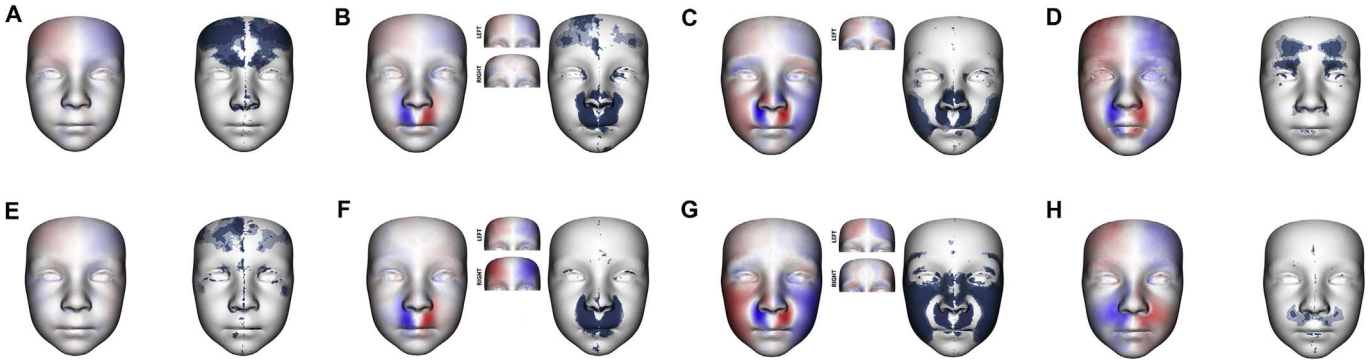

Fig. 2. Color-coded maps and shell distance significance maps of mean asymmetry. The figures on the left show probands at the age of 3 years: (A) controls, (B) UCL (unilateral cleft lip) patients, (C) UCLP (unilateral cleft lip and palate) patients, (D) BCLP (bilateral cleft lip and palate) patients; figures on the right show probands at the age of 4.5 years: (E) controls, (F) UCL patients, (G) UCLP patients, (H) BCLP patients. Mean asymmetry of the forehead in patients with left and right side unilateral clefts in B, C, F, G.

vertex in Morphome3cs to illustrate the areas that caused these results (Fig. 2).

3.1. Controls

Most asymmetry in the controls occurred predominantly in the forehead and medially in upper parts of orbits in both the younger and older age groups (Fig. 2). Positive values of asymmetry were found on the right side. With increasing age, asymmetry diminishes but remains significant, especially in the forehead.

The upper face area showed asymmetry in the buccal region. Significant asymmetry was illustrated only in the lateral parts of the buccal region in the younger category and lateral parts of the zygomatic region in the older category, positive on the left side. In the lower face region, mild inconsistent asymmetry was illustrated on the lower lip.

3.2. Cleft lip patients

Patients with the mildest defect, cleft lip only, showed a similar pattern in both age groups.

The forehead showed the presence of significant positive values of asymmetry on the right side in all age groups except in the right-sided clefts of the three-year-old patients, where the asymmetry was inconsistent (Fig. 2).

In the upper face area (Fig. 2), significant deviations from perfect symmetry were apparent around the *alae nasi*, positive on the opposite side to the cleft. Contrary to this, positive values of asymmetry were found on the opposite side (cleft side) around the nasolabial fold as a continuation of the asymmetry of the philtrum and upper lip (protruding scar). Asymmetry was almost equal in both age categories.

The lower face showed positive deviations from perfect symmetry in the lower lip of the cleft side. Only mild asymmetry of the chin was found and evaluation of the lower face showed no substantial difference between the age categories.

Inspection of symmetry in the nasolabial area revealed an asymmetrical region that created an imaginary triangle, whereby the base was on the upper lip and the apex was adjacent to the *alae nasi*, with more noticeable asymmetry closer to the triangle base in the upper lip.

3.3. Unilateral cleft lip and palate patients

Both left- and right-sided younger groups showed slight asymmetry of the forehead on the right side. Inconsistent asymmetry was found in the right-sided clefts in older category (Fig. 2). Only patients with left-sided clefts in the younger group were evaluated due to small sample in older category (only 3 probands).

The upper face areas (Fig. 2) in patients with complete UCLP were, from the viewpoint of asymmetry, more affected than that of patients with UCL. Significant positive deviations from perfect symmetry were apparent in the area of the *alae nasi* in the non-cleft side and in the area of the philtrum and upper lip in cleft side. In addition to this, positive values of asymmetry found in the buccal region were more marked in older category.

In the lower face area, positive values of asymmetry were found in the lower lip in the cleft side, and were identical in both age categories. There was also visible asymmetry of the chin with positive values on the cleft side.

Once again, asymmetry in the nasolabial area created an imaginary triangle. Conversely, the base of this triangle was in contrast to that of UCL patients, with the base located around the *alae nasi* and the top directed toward the upper lip. More noticeable asymmetry was found once again closer to the triangle base but in this case closer to the *alae nasi*.

3.4. Bilateral cleft lip and palate patients

In patients with complete bilateral cleft, positive deviations from perfect symmetry were found on the right side of the forehead and the upper parts of orbits.

In the upper face region, positive deviations from perfect symmetry were present in the younger group on the left sidewall of the nose continuing inferiorly around the alar base, on the extensive surroundings of the left nasolabial fold and on the left side of the philtrum. The older group showed similar patterns in asymmetry, except the positive asymmetry extended more laterally into the buccal region.

Asymmetry found in the lower face was not consistent within the age categories. In both groups, positive deviations from perfect symmetry were found on the right side of the lower lip. In the older group, positive deviations from perfect symmetry extended in lateral and inferior directions from the cheilion, contrasting with the younger group where we found negative deviations from symmetry. Thus, on the right side of the mandible there were positive deviations from perfect symmetry in the younger group and negative deviations in the older group.

4. Discussion

The objective of this study was to evaluate asymmetry in patients with various severe types of clefts, to assess whether there was a progression of asymmetry in early childhood and to statistically test the differences compared to the control group using progressive 3D technologies.

Unlike other studies that utilized modern 3D techniques and evaluated asymmetry in individuals using color-coded maps [13], performed linear dimensions in patient groups or performed different kinds of shape analysis [11,19–21], our goal was to visualize the differences between observed cleft subgroups and controls, and to identify the areas in the whole face with significant divergences using color-coded maps.

Statistically significant differences between the intervention and control groups were observed within all the cleft groups and confirmed by statistical tests, with the most marked asymmetry found in the UCL and UCLP patients, followed by the BCLP groups. These findings were contrary to the results of [16], who evaluated facial shape, wherein the BCLP group showed more marked differences compared to control group, then the UCL group. This finding indicates that there is no positive correlation between severity of the cleft lip (unilateral/bilateral) and the expression of asymmetry, but implies that unilateral clefts have a different influence on facial asymmetry than bilateral clefts due to the unilateral nature of the defect, which affects both sides and the asymmetry patterns, excluding the upper labial area, which tends to be slightly closer to asymmetry in controls. This statement is in accordance with the findings of Bugaighis et al. (2010) and Bugaighis et al. (2014) [11,22].

Greater variability of facial asymmetry was found in the cleft groups than in the more homogenous control group. Greater variability in the cleft groups was found also in studies examining morphometrics of cleft patients from the point of view of facial morphology as well as palatal shape analysis [11,16,23,24].

In specific regions of the face, most of the cleft subgroups and even the controls demonstrated similar patterns in the asymmetry of the forehead, which is apparently not connected with the orofacial clefts. The basis for this assumption include the presence of positive deviations from perfect symmetry on the right side both in left- and right-sided clefts, and the presence of positive deviations from perfect symmetry on the right side in controls. Asymmetry of the forehead is probably a vestige of the postural/positional plagiocephaly in infant age, where the incidence can reach 50% in infants [25]. It occurs more commonly on the right side [25,26] and leads to the protrusion of the forehead on the side of the occipital flattening [27].

The upper face region in all the cleft groups showed the highest levels of asymmetry. In patients with UCL, asymmetry was mainly found in the nasolabial area, which was directly affected by the cleft. The lateral zygomatic and buccal regions did not show deviations from perfect symmetry. This suggests that the isolated cleft lip and early neonatal lip repair do not cause asymmetry in other regions than the nasolabial region, and do not affect growth of related parts of unaffected maxilla [16]. Younger patients with UCLP also showed asymmetry mainly in the nasolabial region, similar to the UCL group, and showed opposite deviations from the line of symmetry between the *alae nasi* and philtrum. Nasal asymmetry in unilateral cleft defects results from a combination of asymmetry of the underlying skeletal base and muscular diastasis [28]. Deviation of the nasal septum is caused by the unopposed pull of the orbicularis oris muscle and the premaxillary ligament to the caudal nasal septum, which is deviated to the noncleft side nostril leading to the asymmetric, less prominent nasal tip [29]. The lateral nasal cartilage on the cleft side is dysplastic, with shorter medial and longer lateral crus, which results in a less-defined and wider dome [30]. This was evident in all our groups with unilateral defects, who showed negative deviations from perfect symmetry on the cleft side around the *alae nasi*. In bilateral clefts, the nasal septum normally remains midline; however, the less-severe side applies more force to the caudal septum, resulting in deviation to this side [31]. There was only slight asymmetry of the nose in our group compared to the patients with UCL and UCLP.

Nose and lip asymmetry, caused by the initial clefting and subsequent surgical repair, are the most visible deformities in cleft patients. In a study by Borsky et al. (2012) [15], lip symmetry in 97 new-borns who had undergone early neonatal lip repair, was qualitatively evaluated 8–12 months after surgery. This qualitative evaluation showed that the labial contour symmetry was achieved in 68% of cases. However, our assessment using new 3D methods could detect anteroposterior asymmetry in both UCL and UCLP patients, within a few years after this surgery. Positive values of asymmetry were present on the side of the cleft as a slight vestige of the postoperative scar. Hypertrophic scar formation is a postoperative complication of cleft lip [32]. Although studies evaluating nose and lip appearance and wound healing in patients who have undergone early neonatal lip repair reported very good results [15,33–35] anteroposterior asymmetry of the lip is still detectable using 3D morphometrics.

Despite the effects on both sides of the lip in the BCLP group, mild lip asymmetry was found. Unlike the UCL and UCLP groups, similar

deviations from symmetry were detected on the philtrum extending cranially via the *alae nasi* to the nasal bridge region and close surroundings. Russell et al. (2014) [36] also described significant asymmetry of the upper lip in BCLP groups and implied that those findings challenge previous assumptions that patients with bilateral cleft after lip repair are relatively symmetrical.

Slight deviations from perfect symmetry were observed extending laterally in the younger groups with UCLP and BCLP. Older groups with UCLP and BCLP showed an extension of asymmetry laterally to the buccal region, and even to the zygomatic region in UCLP patients. Insufficient maxillary growth after lip repair in patients with UCLP/BCLP, causing different facial morphology compared to healthy controls [16], have been previously demonstrated [37,38]. Palatal shape in patients with UCLP and BCLP were examined in several studies [23,24,39–41] and their results showed that the palate of patients who have undergone surgery are, among other things, more asymmetric than in controls. Rusková et al. (2014) and Šmahel et al. (2004) [24,40] described the shape and asymmetry in patients with UCLP, where the asymmetry patterns with the maximum height of the posterior palatal vault on the noncleft side support our theory that positive deviations from perfect symmetry on the noncleft side in our patients have been formed mainly as a consequence of the skeletal deviations. Šmahel et al. (2009) [41] found that the palatal vault is higher in patients with BCLP than in controls in the anterior direction, but lower in the posterior direction. Asymmetry is present and decreases posteriorly as the palate vault is reduced compared to the controls. Asymmetry of the palatal vault in the patients with BCLP was less noticeable than in the patients with UCLP. This is in accordance with our findings, particularly in older age groups, where the positive deviations from symmetry extended from the nasolabial area to the buccal region and diminished laterally.

In the lower face region, varying degrees of asymmetry were present in all of the groups in the lower lip ipsilateral to the upper lip and were more severe in the patients with UCL but less severe in those with BCLP. Inconsistent symmetry of the lower lip was also found in the controls. Lower lip deformity, which can probably result in asymmetry, can be caused by incorrect positioning of the anterior teeth, which works also as a lip support [42], or as a result of skeletal abnormalities of the mandible or a child's struggle to achieve bilabial closure with the affected upper lip [43].

Positive asymmetry of the chin in the UCLP group was found on the side of the cleft. This finding was in concordance with that of a previous study by Kim et al. (2013) and Lin et al. (2015) [44,45], who showed deviation of the chin to the cleft side; however, the asymmetry was regarded as clinically non-significant. The results of the Kuijpers et al. (2015) [46] study showed significant asymmetry of the chin in the UCLP group compared to controls, and in the UCL group, the asymmetry was lower and nonsignificant. Asymmetry of the chin in five-year-old UCL patients with or without cleft palate was also described by Djordjevic et al. (2014) [13].

Our patients with BCLP had asymmetry of the mandible; however, asymmetry was positive on the right side in younger patients, and negative in the older category. There are studies [47,48] examining mandibular asymmetry in patients with BCLP based on skeletal measurements that showed no significant differences compared to controls. Unfortunately, there are insufficient studies evaluating soft tissue asymmetry in patients with BCLP. Thus, we are unable to sufficiently explain our findings, and the inconsistent asymmetry of the chin between the age groups may also be caused by the small study sample.

5. Conclusion

The aim of our study was to illustrate and evaluate facial asymmetry in two age groups of pre-school kids with various severe orofacial clefts who underwent neonatal cheiloplasty and to compare asymmetry patterns in each group with age-matched healthy controls.

Statistically significant differences were observed in comparison to controls within all the cleft groups. In unilateral clefts, the most noticeable asymmetry was demonstrated in the nasolabial region, which is directly affected by the cleft. The patients with UCL and UCLP had a more protruded upper labial region and less protruded *alae nasi* on the cleft side. In patients with UCLP who also had affected hard and soft palate, asymmetry extended considerably in the lateral direction to the buccal region with age (smaller cheek on the cleft side), which is probably the result of affected maxillary growth. The BCLP groups were characterized by positive asymmetry of the nasolabial region in both the philtrum and the *alae nasi* on the left, and positive asymmetry of the buccal region on the same side in the older age category. This finding indicates that cleft deformity that includes the palate also tends to cause asymmetry of the buccal region; however, the unilateral deformity causes atypical asymmetry, while bilateral defects show asymmetry similar to the controls. With the exception of the buccal region in patients with palatal defects, asymmetry did not increase in the older age category.

Asymmetry of the forehead were found in all the subgroups, more marked in controls and seems to have no connection with cleft deformity.

Overall, we can say that although the aesthetic results of early lip repair are very promising nowadays and the need of additional cosmetic corrections is low, the mild asymmetry of certain parts of the face are still detectable with modern 3D technologies.

Present study could give feedback to the surgeons, how the development of the overall facial asymmetry goes in different cleft defect severity and where and how asymmetry occurs outside the areas directly affected by the cleft.

Conflicts of interest

There are no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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ORIGINAL ARTICLE

Facial Growth and Development in Unilateral Cleft Lip and Palate: Comparison Between Secondary Alveolar Bone Grafting and Primary Periosteoplasty

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Objective: **To describe the effect of secondary alveolar bone grafting in patients with unilateral cleft lip and palate by comparison with a sample of patients who have undergone primary periosteoplasty.**

Design: **Cephalometric analysis of lateral x-ray films in a retrospective semilongitudinal study.**

Patients: **Lateral x-ray films of 18 secondary alveolar bone grafting patients and 48 primary periosteoplasty patients at 10 years of age and again at 15 years of age.**

Settings: **The treatment of secondary alveolar bone grafting patients included lip repair according to Tennison, palatoplasty including retropositioning, pharyngeal flap surgery, and secondary alveolar bone grafting. The lips of primary periosteoplasty patient were repaired using the methods of Tennison and Veau, followed by primary periosteoplasty, palatoplasty including retropositioning, and pharyngeal flap surgery.**

Methods: **Lateral radiographs were assessed using classical morphometry.**

Results: **There were few significant differences at 10 years of age between the secondary alveolar bone grafting and primary periosteoplasty patients. At 15 years of age, there were several significant differences. Compared with primary periosteoplasty patients, subsequent development in patients who had undergone secondary alveolar bone grafting was characterized by a significantly better position of the upper and lower dentoalveolar components in relation to the facial plane, a higher increase in the global convexity of the soft profile, a significantly better maxillary inclination, and a more favorable development of vertical intermaxillary relationships.**

Conclusion: **Craniofacial development in secondary alveolar bone grafting patients was better than that in primary periosteoplasty patients due to the more marked facial convexity, the increased prominence of the nose, and better vertical intermaxillary relationships.**

KEY WORDS: classical morphometry, cleft lip and palate, secondary alveolar bone grafting

Care for patients with orofacial clefts requires a long-term multidisciplinary approach and has a long tradition in the Czech Republic. The approach to treating cleft patients began to progress importantly after World War II (Šmahel et al., 1998). Before secondary alveolar bone grafting (SABG) became the method of choice for reconstructing a defect involving the upper jaw, a cleft defect was reconstructed using primary alveolar bone grafting (PABG), which was gradually replaced by primary periosteoplasty (PP) (Feichtinger et al., 2008).

The PP technique consists of surgical closure of the alveolar cleft with local periosteal flaps. The flap used to bridge the cleft is approximately 5 to 7 mm in width and 15 to 20 mm in length and is obtained from the lateral maxillary segment. The flap is rotated around the medial pedicle and fixed to the posterior premaxillary edge. The flap first joins the cleft jaws elastically and later by bone lamellae. Primary periosteoplasty is usually carried out together with a lip repair (Kuderová et al., 1996). The authors of previous studies have monitored patients after PABG and PP and compared the success of these operations (Šmahel and Müllerová, 1994; Velemínská, 2000).

Secondary alveolar bone grafting, first introduced by Boyne and Sands (1972), has replaced PABG and PP, and today SABG is the most commonly used method for reconstructing the upper alveolar ridge in cleft patients (Feichtinger et al., 2008). From an orthodontic point of view, SABG has become the conventional procedure for

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successful dental reconstruction without the need for prosthetic appliances (Kawakami et al., 2004). It is typically performed at a stage of transitional dentition (between 9 and 11 years of age, before the eruption of the maxillary canines) to allow the corresponding canine to erupt through the grafted site (Newlands, 2000; Dušková, 2007).

Although the main aim of SABG is reconstruction of the upper alveolar ridge, it is possible that this surgery could have an influence on the morphology of some parts of the face that undergo significant changes during development. For this reason, the purpose of the present study was to describe the effect of SABG in patients with unilateral cleft lip and palate (UCLP) by comparison with a sample of patients with the same congenital defects who had undergone PP. Our hypothesis was that there are no differences in craniofacial development in patients after SABG compared with patients after PP.

Our study follows a number of publications that have described the influence of different types of surgery on the development of the craniofacial area performed in the Department of Plastic Surgery at the Faculty Hospital Královské Vinohrady (Šmahel and Müllerová, 1988, 1994; Sameshima et al., 1996; Šmahel et al., 1998). Investigation of the different influence of therapies on patient skull and face development are important for determining the optimal means of reconstructing cleft defects without the need for secondary corrections. Our results will allow comparison between surgical methods and results from other departments and could also prove useful for long-term treatment planning.

Patients and Methods

The current study was based on evaluating the lateral x-ray films of 18 SABG patients (boys) and 48 PP patients (boys); both groups of patients had complete UCLPs without any associated visible malformations.

The study was approved by an ethical committee.

X-ray films were made at approximately 10 years of age (±6 months) and repeated at 15 years of age (±6 months). The SABG patients had a mean age of 10 years 4 months at the time the x-rays were obtained and had a mean age of 15 years 1 month at follow-up. All patients were born between 1988 and 1992 and were treated and operated on using the same methods. In all cases, the lips were repaired with the Tennison method at a mean age of 11 months. The palate was closed using the push-back method with pharyngeal flap surgery at a mean age of 4 years 7 months. The mean age at the time of SABG surgery was 10 years 5 months, with a range of 9 years 3 months to 11 years 9 months.

The mean age of the PP patients was 10 years 1 month at the time of baseline examination and 15 years 1 month at follow-up. All of the PP patients were born between 1972 and 1978. Patient lips were repaired using the Tennison method in 83% of the cases and the Veau method in the remaining 17% of cases, at an average age of 9 months. Both surgical methods were associated with PP using a periosteal flap 5 to 7 mm in width and 15 to 20 mm in length obtained from the lateral maxillary segment. This was followed by a palatoplasty (mean age, 5 years 2 months) in which the push-back method was always used with pharyngeal flap surgery. These patients have been described in more detail in an earlier publication (Velemínská, 2000).

No type of appliances/treatment was used prior to the first lip/lip+PP surgery in SABG and PP patients.

Orthodontic treatment was performed using fixed appliances in 72% of the SABG patients and in 52% of the PP patients. Other patients were treated using removable appliances.

All treatment took place in the Department of Plastic Surgery at the Faculty Hospital Královské Vinohrady by a team of surgeons led by Professor Fára. Both groups of patients were operated on by the same team of surgeons using an identical protocol (excluding SABG and PP surgeries).

X-ray films of both groups of patients (SABG and PP) were obtained under standard conditions (lamp-object distance = 370 cm; object-film = 30 cm; enlargement 8.1%).

The radiographs were evaluated using classical morphometry (Šmahel and Müllerová, 1994). A total of 35 important landmarks were marked on the digitized x-rays (Fig. 1). The landmarks were important for acquiring the cephalometric characteristics in the Craniometrics software application (Velemínská et al., 2004). We measured 92 dimensions, including linear, angular, and dental characteristics, which were necessary for constructing the cephalograms. We selected 28 variables that best characterized the sagittal and vertical skeletal relationships, dentoalveolar relationships, and soft profile. Cephalograms were created using the AutoCAD program.

Statistics

We had four samples for testing: SABG patients at 10 years of age; SABG patients at 15 years of age; PP patients at 10 years of age; and PP patients at 15 years of age.

We first tested basic assumptions, independence, homoskedasticity, and normality. Due to the characteristics of the data, we presumed that the data in each sample were independent and identically distributed (iid). We did not test this assumption because it is true from a theoretical point of view. It was then only necessary to test normality and the equality of variances.

For normality, we used the Shapiro-Wilk and Lilliefors tests. We used the tests on each sample. The normality tests were rather weak and the results from both tests were different. The Lilliefors test did not reject the hypothesis of normally distributed variables, but the Shapiro-Wilk test did so in some cases. We thus decided not to generally presume normality. Due to the

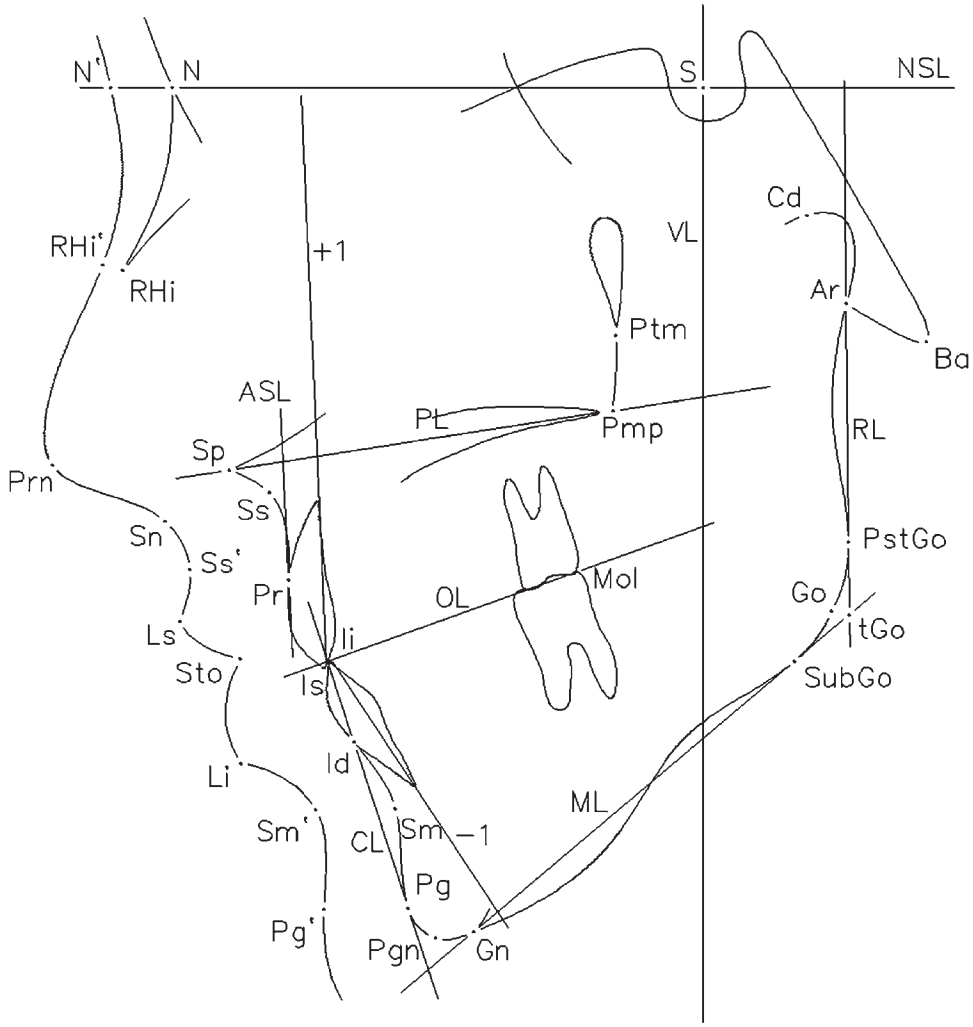

FIGURE 1 Cephalometric points and reference lines used in the present study: Ar (articulare)—intersection of the inferior contour of the clivus and the posterior contour of the ramus; Ba (basion)—most posteroinferior point on the clivus; Cd (condylion)—most superior point on the condylar head; Go (gonion)—point on the angle of the mandible determined by the axis of the ML/RL angle; Gn (gnathion)—lowest point of the mandibular symphysis; Pgn (prognathion)—point on the mandibular symphysis farthest from Cd; Pg (pogonion)—most anterior point on the bony chin; Pg′ (soft pogonion)—most anterior point on the soft chin; Sm (supramentale)—deepest point on the anterior contour of the mandibular symphysis; Sm′ (soft supramentale)—deepest point on the soft contour of the lower jaw; Id (infradentale)—point of gingival contact with the lower central incisor; Ii (incision inferius)—incisal tip of the lower central incisor; Is (incision superius)—incisal tip of the upper central incisor; Mol (molare)—tip of the distal cusp of the lower first molar; Pr (prosthion)—point of gingival contact with the upper central incisor; Ss (subspinale)—deepest point of the subspinal concavity; Ss′ (soft subspinale)—deepest point of the upper lip; Sp (spinale)—tip of the anterior nasal spine; Pmp (pterygomaxillare palatinum)—point of intersection of the palate plane and the fissura pterygomaxillaris; Ptm (pterygomaxillare)—most inferior point of the fossa pterygopalatina where the fissura pterygomaxillaris begins; S (sella)—center of sella turcica; N (nasion)—most anterior point on the frontonasal suture; N′ (soft nasion)—intersection between NSL and the soft profile contour; Rhi (rhinion)—most anteroinferior point on the nasal bone; Rhi′ (soft rhinion)—point on the soft profile contour over Rhi; Prn (pronasale)—point on the top of the apex nasi; Sn (subnasale)—point at which the columella merges with the upper lip; Ls (labrale superius)—margin of the vermilion of the upper lip; Sto (stomion)—point of contact of the upper and lower lips; Li (labrale inferius)—margin of the vermilion of the lower lip; NSL—line through N and S; VL—perpendicular to NSL through S; PL—line through Sp and Pmp; OL—line passing though the midpoint between the incisal tip of the upper and lower central incisors and the posterior cuspid of the first lower molar; +1—axis of the upper incisor; −1—axis of the lower incisor; CL—line through Pg and Id; ASL—tangent to the maxillary alveolar process through Pr; ML—tangent to the mandibular body through Gn; RL—tangent to the mandibular ramus through Ar; tGo (tangenta gonion)—intersection of ML and RL lines.

small number of observations in the two samples, we could not use the central limit theorem.

We also tested the equality of variances between the samples with an *F* test. In the majority of cases, we could not reject the null hypothesis of equality; in the small number of cases in which the null hypothesis could be rejected, this was due to chance or a type I error.

Due to the aforementioned facts, we used a two-sample *t* test (parametric test) and a two-sample Wilcoxon test (nonparametric test) and compared the results. It was necessary to use the nonparametric test

because we did not generally presume normality. In the case of the *t* test, we also computed a *t* test based on the Welch approximation of degrees of freedom, which is used in cases when the variances differ, so as not to underestimate the risk of errors resulting from violation of the equality assumption. The results of this *t* test and of the *t* test for which we assumed the fulfillment of equality of variances were nearly the same. The Wilcoxon test and *t* test produced very similar results, but we decided to use those from the Wilcoxon test, because we were not sure whether the assumptions of the *t* test were met.

An intergroup comparison regarding the changes between 10 and 15 years of age was tested using the two-sample *t* test.

The Dahlberg error was calculated, as were the precision and reliability of the measurements (Harris and Smith, 2009; Šmahel et al., 2009). The coefficients of reliability in 15 selected dimensions were >.98 among all measurements in both samples of SABG and PP patients (Table 1).

The level of significance in the text are indicated by an asterisk following the abbreviation of the relevant dimension (e.g., N-Gn*). Accordingly, 5%, 1%, and 0.1% levels of significance are marked *, **, and ***, respectively.

TABLE 1 Dahlberg Error (SD_E) and Coefficient of Reliability (*R*) of the Measurement*

	PP		*SABG*	
Dimension	SD_E	*R*	SD_E	*R*
N-Sp	0.08	1.00	0.00	1.00
N-Gn	0.12	0.99	0.01	1.00
Sp-Is	0.19	0.99	0.00	1.00
Prn-Sn	0.01	0.99	0.02	1.00
N-S-Pgn	0.12	0.99	0.01	1.00
S-N-Ss	0.08	1.00	0.00	1.00
S-N-Sm	0.20	0.97	0.01	1.00
Pr-N-Id	0.01	1.00	0.02	1.00
N-Ss-Pg	0.05	0.99	0.01	1.00
PL/NSL	0.03	1.00	0.01	1.00
SGo%NGn	0.01	0.99	1.45	0.98
N′-Prn-Pg′	0.05	0.99	1.29	0.99
Is-Ii	0.02	0.99	0.26	1.00
Ls+Li	0.02	1.00	1.30	0.98
NPg-Is	0.02	1.00	1.30	0.98

* PP = primary periosteoplasty; SABG = secondary alveolar bone grafting.

Results

To evaluate the effectiveness of SABG, a group of patients who had undergone SABG was compared with a group of patients who had undergone PP. Our major interest was the area of surgery and the adjacent structures. First, the groups of patients had to be compared before SABG at 10 years of age to determine whether any significant craniofacial growth differences existed.

The main difference between SABG and PP patients at 10 years of age (Fig. 2) was related to the anterior height of the face; specifically, the SABG patients had a greater height of the upper face (e.g., N-Sp***) and thus the whole face (N-Gn*). The height of the lower face was not different (Sp-Pg). This finding was associated with vertical facial disproportionality (NSp%NGn*). Another significant difference was the depth of the nose (Prn-Sn**) in the soft profile (Table 2).

Figure 3 shows a comparison between groups at 15 years of age; the mean values of the monitored dimensions are shown in Table 3, and the intergroup comparison regarding the changes between 10 and 15 years of age is shown in Table 4.

At 15 years of age, there was a persistent divergence between the two groups in the height of the upper face (N-Sp**) and the height of the entire face (N-Gn*). This difference did not increase, but rather diminished slightly. The vertical facial disproportionality (NSp%NGn) was decreased in the PP patients.

Maxillary growth was evident based on an increase in the dentoalveolar height of the maxilla, which was significantly higher in the SABG group (Sp-Is**; Table 4). There was no significant difference in the length or increment of the depth of the maxilla (Ss-Pmp), which was very small in both cases. There was a small insignificant retrusion (S-N-Ss) of the upper jaw (Tables 3 and 4) in both groups. Proclination of the upper alveolar ridge in the SABG patients (ASL/PL) was higher, but not significant.

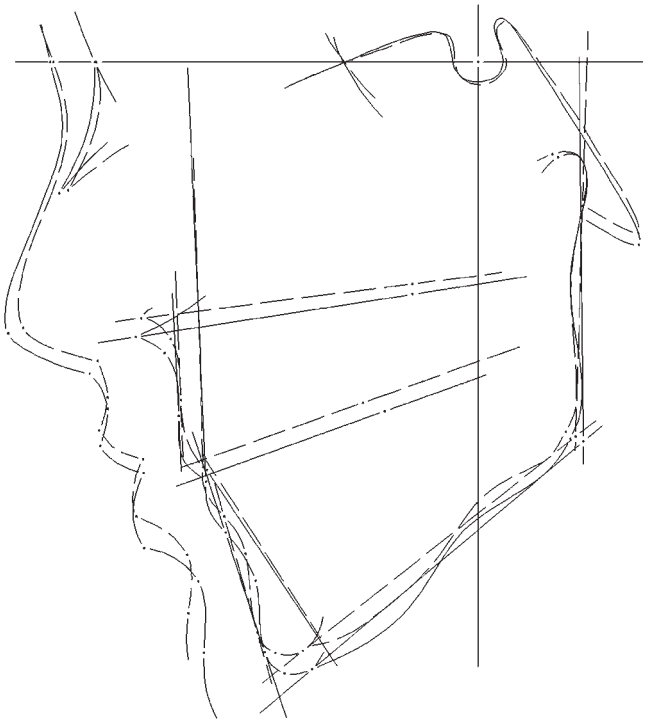

FIGURE 2 Craniofacial comparison of SABG (solid line) and PP (dashed line) patients at 10 years of age. The faciograms are aligned at point S (sella) and the NSL and VL lines. Solid and dashed lines are illustrative.

TABLE 2 Craniofacial Differences Between PP and SABG Patients at the Age of 10

	PP Patients†		*SABG Patients*		
Dimensions	*Mean*	*SD*	*Mean*	*SD*	*P Value*‡
N-Sp (mm)	46.97	2.99	50.17	2.83	.000***
N-Gn (mm)	112.51	6.47	116.29	5.08	.038*
Sp-Is (mm)	28.98	2.66	28.95	3.39	.971
Sp-Pg (mm)	60.36	4.95	61.36	4.89	.467
Ss-Pmp (mm)	44.61	2.61	45.88	2.91	.113
Prn-Sp (mm)	21.29	2.67	22.85	2.92	.075
Prn-Sn (mm)	14.66	1.43	16.38	2.01	.002**
Sn-Ls (mm)	12.46	1.94	13.09	1.86	.317
Sn-Sto (mm)	19.50	2.40	20.32	2.44	.200
N-S-Pgn (°)	71.12	3.70	72.50	3.22	.113
S-N-Ss (°)	75.02	4.15	76.55	3.50	.126
S-N-Sm (°)	73.14	3.34	72.80	2.55	.823
Ss-N-Sm (°)	1.88	3.11	3.75	2.56	.061
Pr-N-Id (°)	1.68	2.34	2.20	2.76	.522
N-Ss-Pg (°)	178.62	6.93	175.03	4.57	.050
PL/NSL (°)	6.63	2.75	8.52	3.75	.059
ML/RL (°)	129.98	5.83	129.50	6.96	.687
PL/ML (°)	31.60	5.19	31.60	6.26	.835
ASL/PL (°)	94.76	9.55	95.91	9.67	.471
SGo%NGn (%)	60.96	3.51	60.21	3.60	.437
NSp%NGn (%)	41.78	2.07	43.16	2.64	.043*
N′-Prn-Pg′ (°)	143.66	6.05	140.40	4.58	.066
Ss′-N′-Sm' (°)	6.01	2.75	6.52	1.56	.741
Is-Ii (mm)	0.75	2.16	0.90	4.57	.283
+1/PL (°)	95.45	7.27	96.26	7.24	.870
Ls+Li (mm)	2.78	2.24	3.06	1.60	.708
NPg-Is (mm)	1.29	3.51	1.65	3.23	.757
NPg-Ii (mm)	0.76	2.91	0.90	2.26	.920

† PP = primary periosteoplasty; SABG = secondary alveolar bone grafting; SD = standard deviation.
‡ *P* value of two-sample Wilcoxon test.
* $P < .05$ ** $P < .01$ *** $P < .001$.

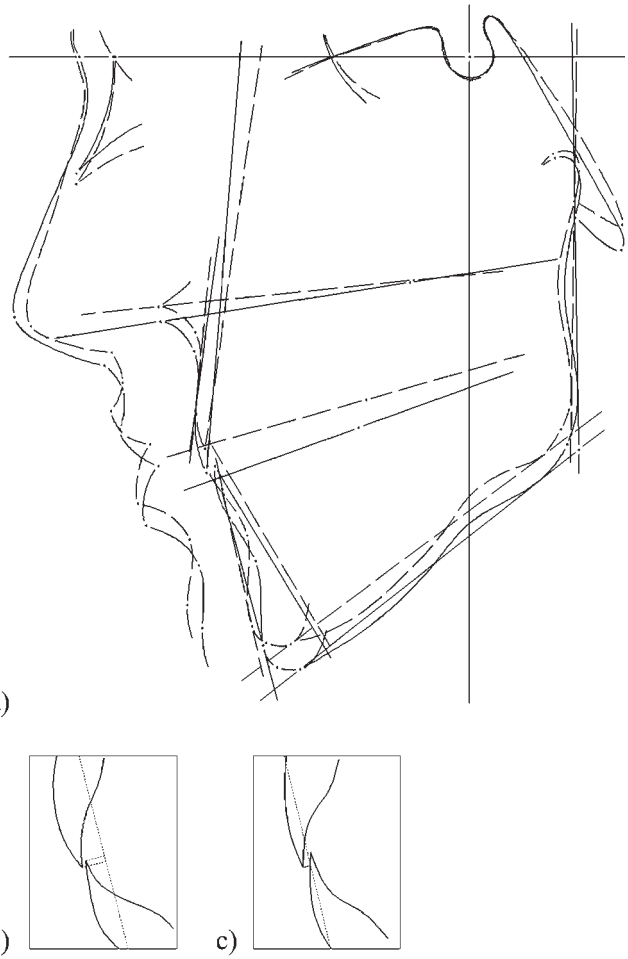

FIGURE 3 Craniofacial comparison of SABG (solid line) and PP (dashed line) patients at 15 years of age. The faciograms are aligned at point S (sella) and the NSL and VL lines. Solid and dashed lines are illustrative. a: Comparison of the skeletal and soft profiles of PP patients (dashed line) with SABG patients (solid line); b: detail of the central incisor position in relation to line NPgL of SABG patients; c: detail of the first incisor position in relation to line NPgL of PP patients.

With respect to the developmental changes in mandibular growth, no significant differences existed. There was also conformity in the slight anterior rotation of the mandible (SGo%NGn) and the unchanged direction of mandibular growth (N-S-Pgn). In the SABG group, as in the PP group, there was a slight, insignificant protrusion of the lower jaw (S-N-Sm).

With respect to facial shape, the difference between the angles describing skeletal convexity (N-Ss-Pg) was unchanged. A significant difference existed in maxillary inclination (PL/NSL**), which was markedly decreased in the PP patients. The maxillary inclination affected the vertical intermaxillary relationships (PL/ML*), which was worse in the PP patients (Table 4).

The differences in the soft profile especially existed with respect the parameters describing the nasal area. Specifically, there was a more marked prominence of the nose (Prn-Sp**) in the SABG group. The difference in the soft part of the nasal depth (Prn-Sn) was evident by 10 years of age, but it increased during the period of observation (Tables 3 and 4). This was related to the decreasing convexity angle (N′-Prn-Pg′**) during development and the significantly more convex profile of SABG patients. The enlarged angle of the soft profile convexity (N′-Prn-Pg′) in the PP patients led to a flattening of the face. Another significantly different dimension was the height of the upper lip (Sn-Sto**), which was smaller in PP patients. The length of the philtrum (Sn-Ls) differed also, being insignificantly shorter in PP patients. The prominence of the upper lip (Ls+Li) was equally decreased in both groups.

The sagittal intermaxillary relationships (Ss-N-Sm, Pr-N-Id, and Ss′-N′-Sm′) were deteriorated in the SABG group, as in the PP group. The vertical intermaxillary relationships (PL/ML*) evolved significantly better in the SABG group during the period of observation. In both groups, treatment led to the maintenance of positive overjet (Is-Ii) during development, which was higher in SABG patients, although not significantly. The upper incisor proclination (+1/PL) increased equally in both groups. The position of the upper and lower incisors in relation to the facial plane (NPg-Is** and NPg-Ii**) in the SABG patients was much better compared with the PP group (Fig. 3b and 3c).

TABLE 3 Craniofacial Differences Between PP and SABG Patients at the Age of 15†

	PP Patients†		*SABG Patients*		
Dimensions	*Mean*	*SD*	*Mean*	*SD*	*P Value‡*
N-Sp (mm)	52.28	3.23	55.47	4.08	.004**
N-Gn (mm)	126.39	7.59	132.04	7.99	.033*
Sp-Is (mm)	30.87	3.69	32.56	3.90	.133
Sp-Pg (mm)	68.71	6.81	70.05	6.17	.453
Ss-Pmp (mm)	46.28	3.00	46.75	3.34	.408
Prn-Sp (mm)	26.56	3.64	30.09	4.65	.007**
Prn-Sn (mm)	17.49	1.97	21.09	3.25	.000***
Sn-Ls (mm)	12.10	2.22	13.54	2.75	.074
Sn-Sto (mm)	20.65	3.16	23.51	2.46	.002**
N-S-Pgn (°)	70.89	4.35	72.52	4.67	.112
S-N-Ss (°)	73.78	4.05	74.67	4.95	.175
S-N-Sm (°)	74.57	3.91	74.26	3.50	.823
Ss-N-Sm (°)	−0.79	3.17	0.41	3.46	.229
Pr-N-Id (°)	−0.07	2.70	1.08	2.34	.169
N-Ss-Pg (°)	185.35	7.40	182.16	7.19	.122
PL/NSL (°)	5.93	3.24	9.01	4.42	.005**
ML/RL (°)	127.69	6.72	127.32	7.34	.977
PL/ML (°)	30.92	6.82	29.33	7.22	.584
ASL/PL (°)	101.69	9.01	106.70	11.93	.131
SGo%NGn (%)	62.71	4.29	62.63	4.10	.857
NSp%NGn (%)	41.44	2.11	42.06	2.16	.071
N′-Prn-Pg′ (°)	141.44	7.14	135.56	7.19	.006**
Ss′-N′-Sm′ (°)	5.07	2.95	5.80	2.71	.801
Is-Ii (mm)	1.16	3.09	1.98	2.43	.360
+1/PL (°)	103.85	7.43	103.43	8.54	.852
Ls+Li (mm)	1.59	2.61	1.19	2.31	.573
NPg-Is (mm)	0.79	4.05	3.51	2.41	.011**
NPg-Ii (mm)	−0.38	3.32	1.97	2.09	.008**

† PP = primary periosteoplasty; SABG = secondary alveolar bone grafting; SD = standard deviation.
‡ *P* value of two-sample Wilcoxon test.
* $P < .05$ ** $P < .01$ *** $P < .001$.

TABLE 4 Intergroup Comparison Regarding the Changes Between 10 and 15 Years of Age

	PP Group† Dif	*SABG Group Dif*	*P Value‡*
N-Sp (mm)	5.31	5.30	.492
N-Gn (mm)	13.88	15.75	.070
Sp-Is (mm)	1.89	3.62	.001**
Sp-Pg (mm)	8.35	8.69	.355
Ss-Pmp (mm)	1.67	0.87	.179
Prn-Sp (mm)	5.26	7.25	.020*
Prn-Sn (mm)	2.83	4.71	.012*
Sn-Ls (mm)	−0.35	0.45	.147
Sn-Sto (mm)	1.15	3.20	.002**
N-S-Pgn (°)	−0.23	0.02	.349
S-N-Ss (°)	−1.24	−1.88	.241
S-N-Sm (°)	1.43	1.46	.480
Ss-N-Sm (°)	−2.67	−3.34	.199
Pr-N-Id (°)	−1.74	−1.12	.142
N-Ss-Pg (°)	6.73	7.13	.401
PL/NSL (°)	−0.70	0.48	.044*
ML/RL (°)	−2.29	−2.18	.451
PL/ML (°)	−0.68	−2.27	.039*
ASL/PL (°)	6.93	10.79	.148
SGo%NGn (%)	1.74	2.42	.626
NSp%NGn (%)	−0.34	−2.55	.000***
N′-Prn-Pg′ (°)	−2.22	−4.84	.022*
Ss′-N′-Sm’ (°)	−0.94	−0.72	.351
Is-Ii (mm)	0.40	1.08	.258
+1/PL (°)	8.40	7.17	.305
Ls+Li (mm)	−1.19	−1.87	.069
NPg-Is (mm)	−0.49	1.86	.012*
NPg-Ii (mm)	−1.14	1.07	.002**

† PP = primary periosteoplasty; SABG = secondary alveolar bone grafting.
‡ *P* value of two-sample *t* test.
* $P < .05$; ** $P < .01$; *** $P < .001$.

Discussion

Currently, SABG is the most commonly used method for reconstructing an alveolar defect. From an orthodontic point of view, SABG has become a regular procedure for successful dental reconstruction without having to use prosthetic appliances (Kawakami et al., 2004).

Secondary alveolar bone grafting has replaced methods used previously, such as PABG and PP. In patients who undergo PABG between the first and third years of life, reduced growth of the maxilla occurs, as does pseudoprognathism and anterior crossbite due to the lack of graft growth (Šmahel and Müllerová, 1994; Dušková et al., 2007). Primary periosteoplasty bridges the cleft using an elastic periosteal flap, which first connects the damaged jaw elastically and later ossifies. Patients undergoing PP show a more marked proclination of the upper dentoalveolar component with restoration of a positive overjet than do patients undergoing PABG (Šmahel and Müllerová, 1994).

More recent studies related to SABG have primarily focused on evaluating eruption of the canines and stability of the graft (Long et al., 1995; Tai et al., 2000; Matsui et al., 2005; Jia et al., 2006; Feichtinger et al., 2007).

The overall development of the faces of UCLP patients after SABG has not been investigated in detail. Brattström (1991) evaluated and compared patients who had undergone different treatment regimes (group A: lip repair, PABG, palatoplasty; group B: presurgical T-traction, lip repair, PABG, palatoplasty; and group C: lip repair, palatoplasty) and patients who had undergone SABG (group SABG: lip repair + vomer flap, palatoplasty). However, these patients underwent vomer flap surgery at 5 months of age, thus midfacial growth could have been affected (Friede and Johanson, 1977), and both boys and girls were included in the study. Another study evaluated the development of the skeletal profile after SABG at a mean age of 8.4 years at the time of surgery, but the range was from 4 to 11 years (Ross, 1987). Other studies followed the effect of SABG on maxillary growth alone (Semb, 1988; Levitt et al., 1999).

Based on these findings, our main aim was to describe the effect of SABG in patients with UCLP by comparison with a sample of patients with the same congenital defect who had undergone PP and to evaluate the presumed influence of SABG on the morphology of the face.

All individuals were operated on in the Department of Plastic Surgery in Prague by the same team of surgeons led by Professor Miroslav Fára, underwent the same treatment, and were metrically evaluated using the same methodology by the same team of researchers.

Patients’ lips were repaired using the Tennison and Veau methods. Based on current studies, we believe that the

different methods of lip repair do not affect the basic structures of the skull and produce differences (Ross, 1987; Šmahel et al., 1998). Furthermore, no significant differences existed between early and late lip repair (Sandberg et al., 2002; Goodacre, 2004; Borský, 2007; Galinier, 2008).

Orthodontic treatment was performed using fixed appliances in more SABG patients (72%) than PP patients (52%). Other patients were treated using removable appliances. Previous studies suggested that there are better overjet (proclination of upper incisors) but worse vertical intermaxillary relationships (PL/ML) in patients with fixed appliances. Worse vertical intermaxillary relationships were associated with the height of the upper lip, which was smaller in these patients (Šmahel et al., 1998; Velemínská, 2000).

Such differences were not found in the current study. Nonsignificant better overjet was caused by proclination of the upper alveolar ridge, not by proclination of the upper incisors. The vertical intermaxillary relationships were better in the SABG patients. Orthodontic treatment certainly affects the growth and position of the upper incisors, but due to the aforementioned findings, we concluded that our results were not affected by a different ratio of using fixed appliances between the SABG and PP groups.

The vertical facial disproportionality increased by approximately 1% in the PP group and 2.5% in the SABG group. The vertical disproportionality in the PP group was still higher at 15 years of age, but not significantly. A noticeable increase in the vertical growth of the lower face, as opposed to limited vertical growth of the upper face, was one of the abnormalities in the development of the cranium in cleft patients. The lower height of the upper jaw was likely of prenatal origin, but growth deviation in the form of increased vertical growth of the lower face developed mainly after palatoplasty as a compensatory adaptation mechanism in response to the deteriorating sagittal intermaxillary relationships (Šmahel and Müllerová, 2000).

The maxilla grew primarily in the vertical direction in the area of the upper alveolar process, and was significantly greater in the SABG group than the PP group. In the Brattström study (1991), SABG patients had a significantly larger anterior height than patients in group A, but smaller than those in group C. A very small increase existed in the depth of the maxilla, both in patients who underwent SABG as well as patients who underwent PP. These results are in agreement with the findings of Levitt et al. (1999), who did not show significant differences in the growth of the maxilla between patients who underwent SABG and patients who underwent PP. There were some differences in the Brattström study (1991); specifically, SABG patients had a significantly smaller maxillary length than patients in group C.

An insignificant difference existed in maxillary inclination, which was higher in the SABG group. The SABG group in the Brattström study (1991) also had better maxillary inclination and maxillary prognathism than groups A and B, but again worse than group C. Brattström (1991) postulated that it was probable that the vomer flap procedure affected maxillary growth. There was no significant difference in maxillary prognathism between the SABG and PP patients in the current study.

With respect to the growth of the mandible, no significant differences existed between groups, even in the mandibular rotation or direction of growth. In the Brattström study (1991) the SABG group also had no differences with respect to the mandible compared with groups A and B; whereas group C had better prognathism and a larger mandible than the SABG group.

The reduction of anterior maxillary growth accompanied by retrusion and simultaneous mandibular protrusion caused by the stronger growth of the mandibular body during the pubertal spurt compared with the growth of the cranial base causes a flattening of the skeletal profile. The convexity of the face in SABG and PP patients decreased nearly evenly. Flattening of the face as a result of maxillary retrusion and mandibular protrusion was another characteristic deviation of craniofacial growth in UCLP patients. This finding was also consistent with the results of Velemínská (2000), Ross (1987), and Šmahel and Brejcha (1985). As a result of the greater growth of the posterior facial height compared with the smaller growth of the anterior facial height, the mandible was slightly rotated anteriorly in SABG patients. The same result occurred in PP patients.

The most significant increase in the SABG group, as well as the PP group, occurred in the soft profile, specifically in the nasal area. The main difference was an increase in the depth of the nose, which was significantly greater in the SABG patients, which led to a relative flattening of the soft profile in PP patients compared with SABG patients. Generally, the main difference in the configuration of the soft profile in SABG patients compared with PP patients was the significantly larger increase in the nasal area in the anterior direction and the resulting greater prominence of the nose. Another difference involved the greater convexity of the soft profile in SABG patients; however, the prominence of the upper lip compared with the prominence of the lower lip was significantly reduced in SABG and PP patients. The reduced height and thickness of the upper lip was a fundamental deviation of the soft profile in UCLP patients (Šmahel and Müllerová, 2000). Similar results were reported by Brattström (1991). The group of patients treated with SABG showed a more prominent nose, as well as a better soft profile than the other three groups.

The dentoalveolar area of SABG patients evolved better than that of PP patients. The sagittal intermaxillary relationship worsened in both groups, but the vertical intermaxillary relationship evolved more favorably in the SABG group. This group also demonstrated significantly better positioning of the upper and lower dentoalveolar

component in relation to the facial plane compared with PP patients.

Conclusion

Our work has brought new information for future orofacial cleft research and clinical practice. The effect of SABG in our sample of patients involved not only successful dental and upper alveolar ridge reconstruction, but also a positive influence on the formation of facial morphology during puberty. Treatment using SABG gave significantly better results compared with previous treatments in which the upper alveolar ridge was reconstructed using PP. The particular benefit of this treatment modality lies in the improved development of the dentoalveolar region and the nose.

The patient profile was more convex than that achieved with any previous surgical procedure and the vertical intermaxillary relationships were also better. Further research in this field is needed to confirm our results.

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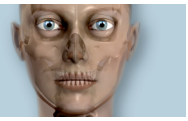

ORIGINAL ARTICLE

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Development of facial sexual dimorphism in children aged between 12 and 15 years: a three-dimensional longitudinal study

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Structured Abstract

Objectives – To evaluate sexual dimorphism of facial form and shape and to describe differences between the average female and male face from 12 to 15 years.

Setting and Sample Population – Overall 120 facial scans from healthy Caucasian children (17 boys, 13 girls) were longitudinally evaluated over a 4-year period between the ages of 12 and 15 years.

Materials and Methods – Facial surface scans were obtained using a three-dimensional optical scanner Vectra-3D. Variation in facial shape and form was evaluated using geometric morphometric and statistical methods (DCA, PCA and permutation test). Average faces were superimposed, and the changes were evaluated using colour-coded maps.

Results – There were no significant sex differences ($p > 0.05$) in shape in any age category and no differences in form in the 12- and 13-year-olds, as the female faces were within the area of male variability. From the age of 14, a slight separation occurred, which was statistically confirmed. The differences were mainly associated with size. Generally boys had more prominent eyebrow ridges, more deeply set eyes, a flatter cheek area, and a more prominent nose and chin area.

Conclusion – The development of facial sexual dimorphism during pubertal growth is connected with ontogenetic allometry.

Key words: 3D imaging; dense correspondence analysis; facial morphology; longitudinal growth; sexual dimorphism

Introduction

The human face shows both individual features and features that are characteristic of a specific group according to age, sex,

ethnicity or health (1). The spatial position and relative proportions of each facial component (e.g. eyes, nose, lips, chin) are mostly determined by underlying genes, but different environmental factors also play important roles.

Accurate and complex quantitative evaluation of facial morphology is of great importance in a variety of scientific fields, especially in a number of biomedical disciplines such as orthodontic and maxillofacial surgery, plastic surgery, and genetics. With regard to pre- and post-operative treatment, comparison of facial differences between patients with craniofacial anomalies or syndromes with normative values as well as comparison between different age and sex groups is important in deciding on an appropriate therapeutic course (2–4). For these purposes, the most valuable and informative reference data are those from longitudinal assessments, which best describe the growth patterns during development.

The degree of sexual dimorphism of the human face changes as a function of age (5). The growth rate is not constant throughout ontogenetic development and differences are also apparent between sexes, especially during the pubertal growth spurt, which occurs approximately 2 years earlier in females (6). In females, craniofacial growth is practically completed by about 13 years of age, while craniofacial growth in males continues into early adulthood (7). The presence of sexual dimorphism in adult facial morphology is apparent (8, 9), but the developmental aspects of facial sex differences are not so clear. The generally accepted view is that the sexual dimorphic facial traits became more apparent after 13 years of age and result from different growth trajectories in males and females (7).

Dense correspondence analysis (10) together with 3D surface imaging systems enables objective study of the whole facial surface. The construction of dense correspondences between 3D surfaces is an accurate method used to support clinical assessment of facial morphology, as well as enables identification of the anatomical structure traits characteristic for a specific group of individuals (e.g. sex- or age-specific features) (11, 12).

Using a 3D optical scanning system together with modern geometric morphometric methods, we hypothesized that this longitudinal approach would help to clarify the development of sexual dimorphism of the human face in adolescence. The primary aim of this study was to analyse the facial form and shape variation of males and females aged from 12 to 15 years to identify the sexual dimorphic traits unique to both groups. The second aim was to evaluate the differences between the average female and the average male face in all age categories.

Subjects and methods

The sample consisted of children from a high school in Kladno and an elementary school in Prague, Czech Republic, who were longitudinally studied between the ages of 12 and 15 years of age from 2009 to 2012 at approximately the same time of the year. Mean age of the subjects was 12.4 years for boys and 12.3 years for girls at the start of the study. The parents of all children were previously informed about the 3D optical scanning procedures and had given their consent to the investigation. The inclusion criteria of the study were Central European origin, body mass index (BMI) within the normal range (13) and absence of craniofacial anomalies, facial trauma or previous orthodontic treatment. Overall, 120 facial scans from 30 children (17 boys, 13 girls) from the original sample of 45 subjects were included in the study because only subjects with a complete series of scans were included.

Scanning and image processing

Three-dimensional facial images were taken using a high-resolution optical scanner Vectra-3D (Canfield Scientific, Inc., Fairfield, NJ, USA) based on stereophotogrammetric technology. The subjects were scanned sitting on a chair. They were instructed to look directly to the front and to relax their face with lips together if possible. The capture time was 2 ms which minimized changes in position or facial expression. The model was imported into RapidForm 2006

software (INUS Technology Inc., Seoul, Korea) for further processing. Finally, each facial model was composed of a triangulated surface mesh with different numbers of vertices.

Dense correspondence analysis

Prior to any other surface-based methods and analysis (i.e. facial averaging, principal component analysis), standardization of all facial models was performed. A dense correspondence algorithm (11, 12) was used to convert all the surface models into polygonal meshes with the same number of vertices by finding mutual correspondences between all facial models.

The first step of dense correspondence analysis (DCA) was to manually place nine reference landmarks on each facial model. One model was selected as the base mesh, and the other models were aligned to it on the basis of 9 reference landmarks (right exocanthion, left exocanthion, right endocanthion, left endocanthion, nasion, pronasale, right cheilion, left cheilion and pogonion). Generalized Procrustes analysis (GPA) was used to register the landmarks by removing translational and rotational (14) differences from the data. GPA enables either normalizing the models to equal sizes or preserving the size. The mean position of each landmark was computed. Each surface model was then warped into the mean position of the reference landmarks using the thin-plate spline (TPS) technique (14). Correspondences between the vertices of the base mesh and points in other meshes were found based on the closest point principle. Finally, all the surface models were unwrapped back to their original position by inverse TPS taking the points of correspondence with them. In this way, all of the surface meshes had the same number of vertices, which could be used as landmarks for further analysis. DCA is part of the subroutine of in-house Morphome3cs software (http://cgg.mff.cuni.cz/trac/morpho).

Facial averaging

The average facial shell for each specific group was created using the tools available within Morphome3cs software (including DCA, GPA without normalizing the size). Finally, four average male facial shells and four female facial shells, one each at ages 12, 13, 14 and 15, were constructed. The average faces were then imported to RapidForm 2006, where morphologic differences between all pairs of sex-specific faces were compared using a specialized superimposition technique, which has been used and described previously (15). The parameters used in our study were colour deviation maps and histogram plots, which were used to visualize and quantify areas of difference between two average facial shells. In each age category, the average female face was used as the initial (reference) shell. Generally, the more protrusive parts of the female faces were represented in red. The parts which were situated more deeply, compared to the male faces, were in blue and vice versa. The tolerance level was set at 0.5 mm, and areas with deviation below this threshold were represented in black and were considered to be similar.

Shape and form analysis

Principal component analysis (PCA) was used to explore the relationships between groups of males and females in each age category and also to analyse their variability. PCA was performed both with and without normalizing size to evaluate the variability of facial shape and form. The study was mainly focused on those components that distinguish males and females in each age category in the best possible way, that is those that most markedly exhibit sexual dimorphism. The analysis was supplemented by PCA scatter plot, which was used to visually represent variation among the individuals in the sample for a selected pair of principal components (PCs).

Multivariate permutation testing of PCA scores (16) was used to assess statistically significant differences in facial shape and form between the groups. The significance level was set at 0.05. The broken-stick criterion (17) was used to determine the number of statistically significant components included in the analysis. PCA and

permutation testing were performed in Morphome3cs.

Results

Analysis of facial form

First, variability of facial form in boys and girls aged 12–15 was evaluated in the pooled sample. Table 1 shows a summary of the statistically significant PCA components according to the broken-stick criterion, which explained from 62.5% to 72.2% of variability. However, sexual differences in each age category (Fig. 1) were best characterized using the first two components (PC1 and PC2), which together were responsible for more than 50% of the total variability in facial form (specifically 53.4%, 55%, 55.3% and 52.4%, respectively, from age 12 to age 15). PCA scatter plots (Fig. 1) show the relationship between PC1 and PC2 components and allow visualization of the distribution within each age and sex subgroup. Generally, the variation of facial form was greater in boys in all age categories with the exception of 14-year-old subjects, where variability was similar for both sexes. The PCA scatter plots further showed a high degree of overlap in the distribution of individuals in the 12- and 13-year-old groups, indicating that boys and girls were indistinguishable in these age categories. In the 14-year-old group, PC1 slightly separated boys and girls, and in the 15-year-old group, the separation became much more evident.

The results of a multivariate permutation test of PCA scores are shown in Table 2. Statistically significant differences in facial form between boys and girls were found only in the 14- and 15-year-old categories.

Superimposition was used to evaluate differences between the average male face and the average female face from 12 to 15 years. Visual comparisons are shown as colour-coded maps together with histogram plots, which display objective differences between paired average faces (Fig. 2). A decrease in the black areas was apparent (from 36.08% at age 12 to 18.34% at age 15) which indicated increased highlighting of sexual differences with age. Comparison of the average faces from the lateral view shows that the lower third of the average male face is longer in all age categories compared to females (Fig. 2). As a result, female faces appear to have relatively more protruding lower lips and anterior parts of the chin (in colour-coded maps), but in fact, these areas were situated within the supramental concavity of average male faces.

Table 1. **Principal component analysis components of facial form and shape of boys and girls aged 12–15 according to the broken-stick criterion**

Age categories	12 years		13 years		14 years		15 years	
	% of variability		% of variability		% of variability		% of variability	
Number of components	Form	Shape	Form	Shape	Form	Shape	Form	Shape
1	38.4	25.0	41.5	19.7	39.2	25.1	34.2	24.5
2	15.0	12.9	13.5	16.2	16.1	14.7	18.3	15.6
3	8.9	11.5	8.2	12.2	9.6	13.8	10.0	11.6
4	6.6	8.9	5.5	8.9	7.3	10.1		9.2
5		7.5		7.0				7.2
6		6.7		6.1				
7				5.7				
∑	68.9	72.5	68.7	75.8	72.2	63.7	62.5	68.0

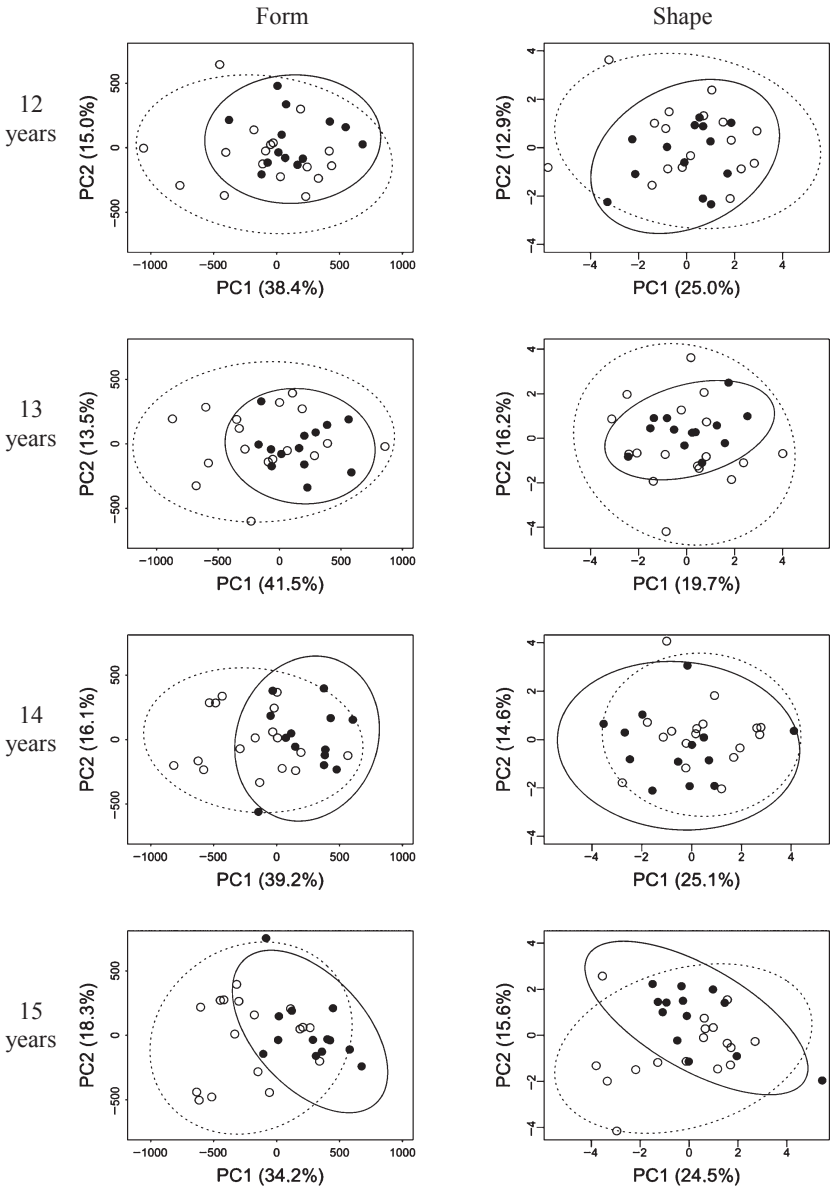

Fig. 1. Scatter plots of the PC scores of boys and girls with respect to form (left) and shape (right). The *x*-axes are the first components (PC1) and the *y*-axes are the second components (PC2). The white points represent boys, and the black circles represent girls. The confidence ellipses include 95% of the individuals in each subgroup.

In the 12-year-old group, the upper third of the average female face was longer compared to males. The female face tended to have a more anteriorly situated eye region. In contrast, males showed more marked protrusion of the lateral part of the forehead and the eyebrow ridges, as well as the nostril region, philtrum and upper lip.

In the 13-year-old group, the upper third of the average female face was still slightly longer and was also more protrusive in the central part of the forehead. The deeper situated eye region in males became more obvious compared to age 12, and the central sections of the cheeks were more prominent in girls. The boys had on average a larger and more protruding nose tip, nostrils, area below the nose, upper lip and areas around the corners of the mouth. The chin region showed more marked protrusion compared to age 12. These differences can be seen more clearly in profile view (Fig. 2).

In 14-year-old girls, there were no apparent differences compared to the previous age category, except for a more protruding cheek region, which became more evident and enlarged in downward projection. There was a visible increase in nose prominence connected with a downward shift of both upper and lower lips in boys.

In the 15-year-old category, the sexual dimorphic differences in favour of girls were again apparent in the eye region and the cheeks. The greater and more protrusive parts of the face in favour of boys were the forehead (except the central part), eyebrow ridges including the glabellar area, the entire nasal region, upper lip and mandibular area.

Table 2. **Comparison of facial shape and form differences between males and females using permutation tests**

Age category	Number of components*		*p*-value	
	Form	Shape	Form	Shape
12	4	6	0.188	0.230
13	3	7	0.122	0.333
14	4	4	0.019	0.136
15	3	5	0.003	0.109

*Number of components included to the analysis according to the broken-stick criterion.

Analysis of facial shape

In this study, only variability in the facial shape was evaluated, because no significant sexual dimorphism in shape was found. Table 1 shows a summary of those PCA components which corresponded to the broken-stick criterion. These components explained from 63.7% to 75.8% of variability in total facial shape. PC1 and PC2 described on average 38.4% of the total variability (specifically 37.9%, 35.9%, 39.7% and 40.1% at ages 12 to 15). PCA scatter plots (Fig. 1) show

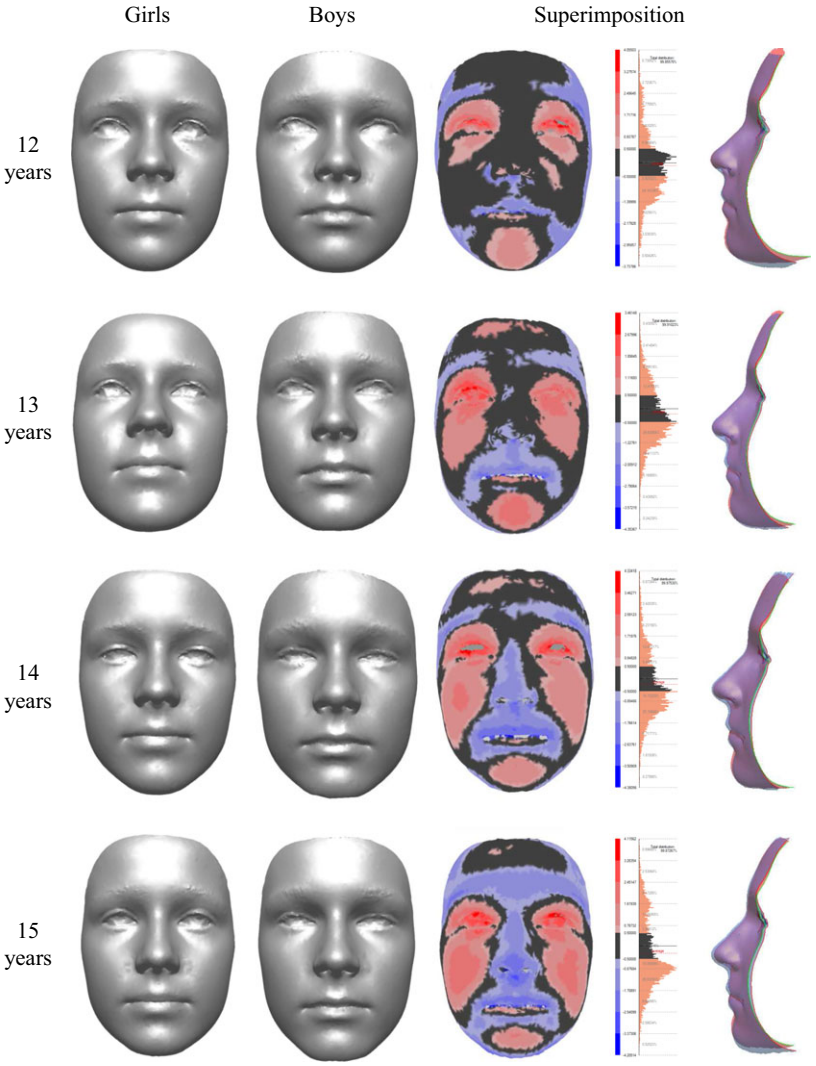

Fig. 2. Average facial shells for girls (left) and boys (centre) in each age category and their superimposition within the same age category. Superimposition is represented by colour deviation maps, supplemented with histogram plots and lateral views of transparent facial surfaces (right). The histogram plots show the differences in the colour maps. The more protrusive parts of the average female faces are represented in red, while the parts which are situated more deeply, compared to male faces, are coloured blue and vice versa in males. Black represents the areas below the tolerance level of 0.5 mm. The percentages of black areas were 36.08%, 31.21%, 24.73% and 18.34% at ages 12, 13, 14 and 15.

the relationship between the first and second components and visualize the distribution within each subgroup. Generally, variability in facial shape was greater in boys in all age categories with the exception of 14-year-old subjects, where the variability was similar for both sexes. The PCA scatter plots further show a high degree of overlap in the distribution of individuals at ages 12, 13 and 14 and indicate no overall shape differences. In the 15-year-old group, PC1 slightly separated boys and girls.

The results of multivariate permutation testing of PCA scores are shown in Table 2. No statistically significant differences in facial shape between boys and girls were found in any age category, so visual evaluation of facial shape was not performed.

Overall, statistically significant sexual differences in facial morphology were found only in the 14- and 15-year-old categories with respect to form, while facial shape differences were not observed in any age category.

Discussion

In the present longitudinal study, a 3D optical scanning system and its applications together with modern geometric morphometric methods (GMM) were used to describe the development of facial sexual dimorphism in children between 12 and 15 years of age. Previous longitudinal studies describing the sex-related facial differences during growth were mostly based on direct linear measurement of the face (18) or on X-ray films (19, 20). These studies provide valuable information about the growth of individual dimensions, but fail to capture the essence of the face as a three-dimensional structure. The 3D imaging systems used in our study overcome some of the limitations of such 2D methods, because salient features of the facial form as a whole are overlooked (21).

Variation in facial shape and form

According to the distribution of individuals, no clear differences in variation between the two sexes were found in any of the observed age categories with respect to facial shape (Fig. 1). Previous cross-sectional studies of soft-tissue facial surfaces showed no significant differences in overall facial shape in the 8- to 12-year-old group (22) and slight but non-significant differences in the shape of the lower facial third during puberty (23). This is in contrast to a longitudinal craniofacial study carried out by Bulygina et al. (24), who found that differences in facial shape occur from age 12, when growth trajectories in males and females exhibit some degree of divergence.

In terms of facial form, the separation of both sexes was observed from 14 years of age and became more apparent in the 15-year-old age category, which was confirmed statistically. This sex differentiation was obtained using the first component (PC1), which is usually interpreted as a measure of size, while all the other components are interpreted as measures of shape and this association between size and shape during growth is connected with ontogenetic allometry (25). Facial form therefore more closely reflects the development of facial sexual dimorphism than facial shape.

Sex differences in various facial parts

In terms of the upper third of the face, the average female faces were found to have a larger forehead in the lateral view in the 12- and 13-year-old age groups. These findings correspond with those of several previous studies (23, 26). The most noticeable differences in this area were found in the eyebrow ridges. Their lateral parts were more prominent in boys from 12 years of age and the prominence increased with age up to 15 years, when the prominence extended up to the glabellar area. In a slightly older age group (15.5 years), prominence of the eyebrow ridges was observed only in the lateral areas (27). In association with the more prominent supraorbital part, eyes were situated more deeply in relation to the facial plane in boys compared to girls in all age categories. One possible explanation is that sinus enlargement in conjunction with size differences in certain areas of the orbit might cause this difference in the prominence of

the glabella and eyebrow ridges (9). Deeply situated eyes in males were also found in the study population aged 15.5 years (27), as well as in adult facial morphology (8).

In the middle third of the face, differences were mainly evident in the cheeks and nose. The cheeks were protruded more in girls, which corresponding with the increase in facial (buccal) fat during puberty, which is generally much more evident in females (28). On the other hand, males had flatter cheeks in all age categories, probably due to their wider frontal and zygomatic processes (29). The most distinctive differences were observed in the nasal region. While in the 12-year-old group, no or minimal sex-related differences were found, each part of the nose subsequently enlarged with age. These results correspond with previous 2D (30) and 3D studies (27, 31). According to the hypothesis of Rosas and Bastir (32), the size of the nose and nostril soft tissues could be important in meeting the greater oxygen requirements of males.

Overall, elongation of the nose also affected the area of the philtrum and upper lip, which were more prominent in boys in all age categories, with prominence increasing with age. The same results have also been described in similar studies (27, 31). In younger age groups (below 12 years), a fuller and more prominent upper lip was found in girls (22). We also observed a greater prominence of the lower lip vermillion area in girls in all age categories and a more prominent lower lip in boys from 14 years. These differences could be observed in the lateral view (Fig. 2). If male and female average faces were ideally superimposed according to the lip area, the whole lower lip would be more prominent in boys. A more prominent lower lip in boys has also been described in the slightly older age group (15.5) (27). After 13 years of age, an overall elongation of the lower face in boys occurred, but due to the shift of the compared parts, female faces appeared to have a relatively more protruding anterior part of the chin, but from the lateral point of view, these parts were situated within the male supramental concavity. Lengthening of the lower face was mainly due to pubertal growth of the mandible, which has been described in previous studies (24, 33). One of the reasons for the more prominent mandibular region is that the male muscles, which are stronger compared to female muscles, produce greater forces that affect mandibular growth (34).

Increasing size and shape (form) of facial features during puberty is associated with a high testosterone-to-oestrogen ratio (T/E ratio) (35). Direct measurement of plasma testosterone levels in boys during puberty shows its increase with age, which results in larger and more robust male faces compared to girls with mild sexual ontogenetic allometric divergence (36). The onset of puberty occurs about 2 years earlier in females and the growth spurt slows down at about 13 years of age (7, 24), while male growth peaks at 15 years of age (37), so males take longer to achieve full facial development and their features appear more distinct (36).

Conclusions

1. Facial sexual dimorphism became more evident during pubertal growth (from 12 to 15 years). Significant sexual differences in facial form were found, but only in the 14- and 15-year-old categories.
2. No significant sexual differences in facial shape were found between 12 and 15 years.
3. The variability of facial form was greater in boys at ages 12 and 13; the female faces were within the variability of the male faces, indicating that boys and girls are indistinguishable in these age categories. At age 14, a slight separation between boys and girls was found and this separation became more evident at age 15.
4. Three-dimensional surface-based analysis together with geometric morphometric methods provides a qualitative and quantitative non-invasive technique for studying facial morphology.

Clinical relevance

Sexual dimorphism of facial morphology is clearly present in adults, but the developmental

aspects are not so clear. In this longitudinal study, a three-dimensional optical scanning system and its applications together with modern geometric morphometric methods (DCA, PCA) were used to provide a detailed analysis of the facial surface as a whole, leading to a better understanding of differences between the two sexes during pubertal growth. Knowledge of the longitudinal development of sexual dimorphism is beneficial for evaluation of different facial anomalies and syndromes as well as orthodontics or plastic surgery.

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