

ABSTRACT

Background: Achalasia is a primary esophageal motility disorder that can be classified into three types (I-III) based on high-resolution manometry (HRM). Exact pathogenesis is unknown, but immune-mediated processes and genetic predisposition play a role, which is supported by finding of a genetic risk variant (rs28688207 insertion) in HLA-DQB1 gene that is strongly associated with achalasia. Per-oral endoscopic myotomy (POEM) has become a standard treatment for achalasia, but the long-term efficacy, safety and impact on esophageal physiology are not fully understood. The aims of our studies were to perform the first genotype-phenotype analysis investigating the frequency of rs28688207 across three HRM types of achalasia, to evaluate the efficacy and safety of POEM and to assess the post-POEM esophageal motility patterns.

Patients and methods: These were three retrospective studies of prospectively collected data. Genotyping of the rs28688207 insertion was performed using real-time PCR in 347 patients from Czech Republic ($n = 163$), Germany ($n = 114$), Greece ($n = 70$). The efficacy and safety of POEM were evaluated in 133 patients treated in our center. The post-POEM esophageal motility was assessed using the Chicago Classification in 237 patients in whom HRM was performed prior to and after POEM.

Results: The frequency of the rs28688207 insertion was significantly different across achalasia types ($p = 0.038$), being most prevalent in type I (14.6 %) vs. type II (9.5 %) and III (6.3 %). POEM was successfully completed in 132 (132/133; 99.2 %) patients, only one serious adverse event occurred. Treatment success at 3, 12, and 24 months was 95.5 % (CI 89.6-98.1), 93.4 % (86.5-96.8), and 84.0 % (71.4-91.4), respectively. Pathological gastroesophageal reflux was observed in 41.5% of patients after POEM. Altogether 68 patients (68/237, 28.7 %) had signs of contractile activity after POEM, newly appearing in 47 patients (47/214, 22.9 %). In these patients the pre-POEM IRP, LESF and post-POEM IRP were significantly higher than in the patients without contractions. Peristaltic recovery was more frequent in type II achalasia ($p=0.097$). The post-POEM Eckardt score and emptying of the esophagus (assessed by fluoroscopy) did not significantly differ between the groups with and without contractions after POEM.

Conclusions: 1. The HLA-DQB1 risk allele was most prevalent in type I, suggesting the role of immune mechanisms triggered by the insertion on the more rapid disease progression of type I. 2. POEM is highly effective and safe treatment method for achalasia with treatment success in >84 % at 24 months. The disadvantage may be the post-POEM reflux present in about 40 % of patients. 3. More than 20 % of achalasia patients have signs of partial recovery of esophageal

peristalsis after POEM, which occurs more frequently in type II achalasia, although it seems to be clinically irrelevant.