Dysphagia with fatal choking in oculopharyngeal muscular dystrophy
Case report

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Abstract

Rationale: Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant late-onset progressive muscle disorder typically characterized by ptosis, difficulty in swallowing, and proximal limb weakness. Underdiagnosis of OPMD is common in Asian countries and results in delayed diagnoses and fatal events.

Patient concerns: Here, we report the case of a 53-year-old female who suffered from progressive dysphagia and experienced several choking events involving solid material. An extensive family history of dysphagia was noted, and 2 family members had died as a result of aspiration.

Diagnosis: PABPN1 genotyping and DNA sequence analysis revealed a heterozygous $(GCG)_{10}(GCA)_3GCG$ mutation that led to the diagnosis of OPMD.

Interventions: Rehabilitation exercises, namely, the Shaker exercise and the Masako maneuver, were suggested.

Outcomes: Improved swallowing ability with safe food intake was noted after 2 months of training. Surgical intervention will be considered when progression of the disease is noted.

Lessons: Underdiagnosis and a lack of awareness of OPMD may lead to choking, aspiration pneumonia, and death in multiple members of affected families. Currently, there is no definitive treatment for OPMD, but rehabilitation exercises and surgical intervention are helpful in relieving dysphagia.

Abbreviations: DNA = deoxyribonucleic acid, OPMD = oculopharyngeal muscular dystrophy, PABPN1 = poly A binding protein nuclear 1, RNA = ribonucleic acid.

Keywords: dysphagia, masako maneuver, oculopharyngeal muscular dystrophy, shaker exercise

1. Introduction

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant late-onset progressive muscle disorder typically characterized by ptosis, difficulty in swallowing, and proximal

limb weakness.[1] The standard method of diagnosing OPMD is gene testing. OPMD is caused by the abnormal increase in the number of repeats of the alanine-encoding (GCN) trinucleotide in the *PABPN1* gene.[2] The wild-type PABPN1 gene contains 10 GCN repeats, whereas affected individuals have 11 to 18 repeats.[3]

OPMD has been reported worldwide, with the highest prevalence in Bukhara Jews (1:600)[4] and French Canadians (1:1000). However, only few small cohorts have been reported in the Chinese population. Families with the $(GCG)_9(GCA)_3GCG$ mutation and the $(GCG)_6(GCA)(GCG)_4(GCA)_3GCG$ mutation were reported by Huang et al[5] and Kuo et al.[6]

Here, we report a case of OPMD with the $(GCG)_{10}(GCA)_3GCG$ mutation. The patient had an extensive family history of dysphagia and lethal choking events. Owing to the lack of knowledge of the disease and a greater concern about the ethical issues related to gene analysis in Asian societies, OPMD may have long been underdiagnosed in Eastern and Southeastern Asia. Dysphagia and aspiration are important issues that cannot be neglected among these patients.

2. Case presentation

A 53-year-old Taiwanese female was referred to our Otolaryngology and Neurology department because of progressive dysphagia. She had been healthy until 6 years ago, when she developed ptosis and dysphagia.

Figure 1. Pedigree of the family. The family tree shows the affected (black) and asymptomatic (blank) members. Squares indicate males, and circles indicate females. An autosomal dominant inheritance pattern can be seen in the pedigree. III-8 is the proband (arrow). II-4, II-6, and III-8 underwent blepharoplasty because of progressing ptosis. I-2 and II-1 died of choking events related to the disease.

The ptosis progressed gradually, causing her to have trouble with driving. Three years ago, blepharoplasty was recommended and performed by a plastic surgeon. Two choking events with solid food recently occurred, prompting her to seek our assistance. An extensive family history of choking and dysphagia was revealed in her interview. The affected family members are shown in Figure 1, and an autosomal dominant inheritance pattern was revealed. II-1, II-4, and II-6 suffered from ptosis and received blepharoplasty. Her grandmother (I-2 in Fig. 1) and older brother (II-1 in Fig. 1) died from choking events.

The physical examination was unremarkable. Nasopharyngoscopy showed saliva pooling at bilateral pyriform sinus. Effort swallowing was observed while food intake. A video fluoroscopic

swallowing study (Fig. 2) showed laryngeal vestibule invasion, indicating unsafe swallowing with a Rosenbek Penetration-Aspiration Scale score of 4. Prolonged and inefficient swallowing with pharyngeal residue at vallecula and bilateral pyriform sinus was noted while testing nectar-thickness, Honey-thickness, and Pudding-thickness materials. Poor laryngeal elevation and difficult cricopharyngeal opening were demonstrated throughout the swallowing process. Considering the clinical presentation of ptosis and dysphagia, OPMD was suspected. PABPN1 DNA Fragment Analysis[7] (Fig. 3) and sequence analysis (Fig. 4) were conducted by Applied Biosystems 3730XL DNA Analyzer. Although the wild-type PABPN1 gene at this locus should contain 2 copies of $(GCG)_6(GCA)_3(GCG)_1$, the sequencing analysis revealed 1 allele with $(GCG)_6(GCA)_3(GCG)_1$, and 1 allele with a mutated $(GCG)_{10}(GCA)_3(GCG)_1$ sequence. The abnormal polyalanine expansion at PABPN1 confirmed the diagnosis of OPMD. The study was approved by the hospital's Institutional Review Board (CCH IRB No. 110407). Informed consent for publication was obtained from the patient as well.

The patient was then referred to speech language pathologists for further rehabilitation exercises. The suggested twice daily exercises were 3 repetitions of the Shaker exercise[8] and the Masako maneuver.[9] The patient's symptoms improved, and a solid diet was tolerated after 2 months of training. Because OPMD is a progressive disease, cricopharyngeal dilatation will be the next treatment choice if the dysphagia worsens.

3. Discussion

OPMD is an autosomal dominant degenerative disease caused by PABPN1 polyalanine expansion. Compared with unaffected individuals who have 10 repeats of alanine in the *PABPN1* gene, affected individuals have an abnormal expansion to 11 to 18 repeats of alanine, causing misfolding of the protein and insoluble aggregation in the nucleus. Although the relationship between the PABPN1 polyalanine expansion and the symptoms of OPMD has long been questioned, a recent large cohort study[3] involving 354 patients in France demonstrated that OPMD patients with longer PABPN1 polyalanine expansions are diagnosed at an earlier age. These patients may suffer from an earlier onset of the disease and more severe symptoms than those with shorter polyalanine expansions.
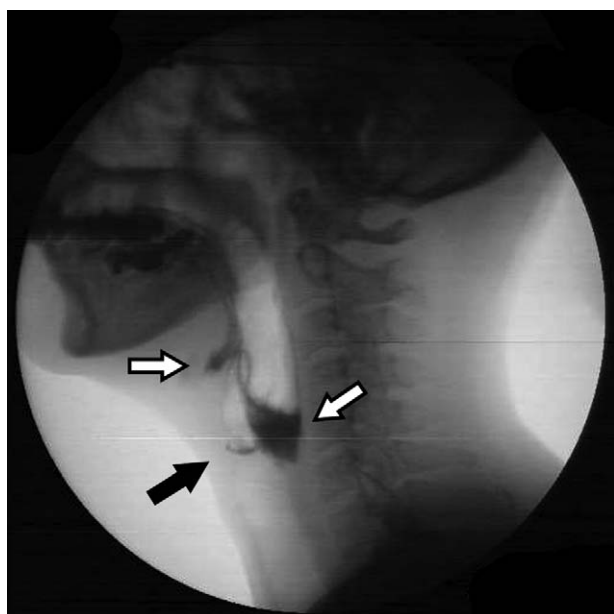
Figure 2. Results of the video fluoroscopic swallowing study. Material contact with vocal cord (black arrow) can be seen in the video fluoroscopic swallowing study before the commencement of the rehabilitation program. Much vallecular and pyriform sinus residue (white arrow) can be seen in the video clip. Upper esophageal sphincter dysfunction and poor laryngeal elevation are common findings noted in video fluoroscopic swallowing studies of OPMD patients.
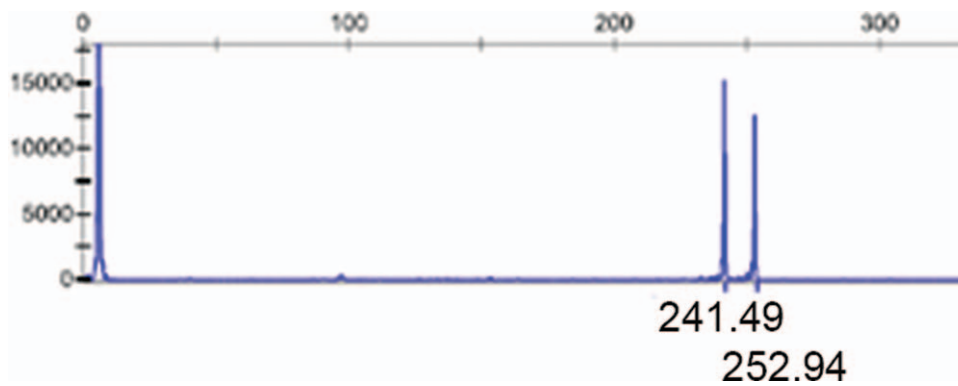
Figure 3. PABPN1 DNA fragment analysis. Numbers beneath each peak is the estimated size of DNA fragments. *PABPN1* genotyping from the patient showed one allele with normal $(GCG)_6(GCA)_3(GCG)_1$ sequence with fragment of 241.49 (241 base pair), and one allele with mutated $(GCG)_{10}(GCA)_3(GCG)_1$ sequence, 252.94 (253 base pair), which is 12 base pair longer.

A dysphagia profile investigation of OPMD patients was conducted by Tabor et al.[10] The study involved 22 OPMD patients and 124 video fluoroscopic swallowing evaluation clips, and it was determined that 86.3% of the swallows were characterized as inefficient. Vallecular residue was present in 77.3% patients, and piriform sinus residue was observed in 90.1% patients. Penetration or aspiration was noted in 33% of the swallows, leading to inadequate airway protection. A significant association between incomplete epiglottis inversion and airway safety was also demonstrated among OPMD patients. Proper exercise programs including the Shaker exercise or Mendelsohn maneuver are helpful in such circumstances by improving laryngeal lifting, cricopharyngeal opening, and epiglottis inversion. The Shaker exercise and the Masako maneuver are swallowing rehabilitation exercises that strengthen the swallowing muscles, whereas the Mendelsohn maneuver helps with swallowing food. The Mendelsohn maneuver required more muscle effort and decreases the pre-swallowing upper esophageal sphincter pressure,[11] whereas the Shaker exercise helps eliminate pharyngeal residue and decreases post-swallowing aspiration.[8] Tongue-holding exercises,[9] such as the Masako maneuver, strengthen the muscle at the base of the tongue and improves the coordination between the hyoid bone and the larynx, thereby improving pharyngeal constriction.
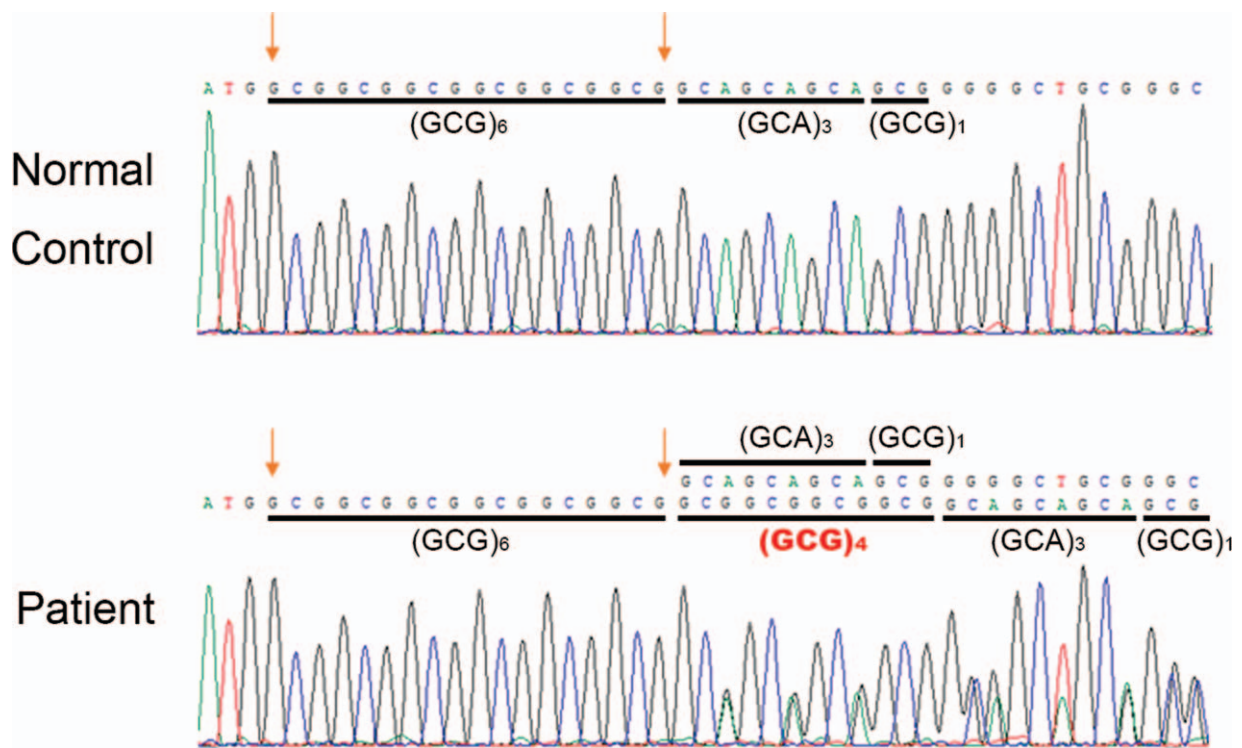
Figure 4. Sequence analysis of genomic DNA. The patient's heterozygous $(GCG)_{10}(GCA)_3(GCG)_1$ expansion is compared with the homozygous *PABPN1* gene sequence in healthy individuals. Within the red arrows are the normal $(GCG)_6$ sequence. Note the frameshift mutation of $(GCG)_4$ started after the red arrow in the abnormal allele.

Currently, there is no effective treatment for OPMD-related dysphagia. Cricopharyngeal dilatation, botulinum toxin injection, and myotomy are common procedures used to treat cricopharyngeal dysfunction. Cricopharyngeal dilatation, either by bougienage or balloon, is less invasive and has been used for decades. Gradual bouginaton can be performed in clinics without anesthesia. More aggressive dilatation with a large-bore bougie[12] or balloon can be performed endoscopically under general anesthesia. A systematic review[13] noted that although the mean success rate of myotomy (78%) is higher than that of dilatation (73%) and that of botulinum toxin injection (69%), the difference between the success rates of myotomy and dilatation is not statistically significant. Considering the benefits of a less-invasive and more feasible procedure, dilatation can be a suitable choice for patients who cannot undergo myotomy or botulinum toxin injection.

Botulinum toxin injection has been used as a test to determine whether myotomy will be effective. Recently, it has also been used as an alternative treatment for upper esophageal sphincter dysfunction. Botulinum toxin injection can be performed under general anesthesia by transcervical surgery with endoscopic assistance. Percutaneous injection with electromyographic guidance[14] has also been reported with the benefits of local anesthesia and a shorter operating time. The dose of botulinum toxin ranges between 0~100 units. The logistic regression analysis in the systematic review indicated that a 20-unit increase in the midpoint dose increases the odds of the success of the procedure.[13] The complication rate reported in literature reviews is, and the reported complication are mainly temporary unilateral vocal cord palsy,[14] dysphonia, or worsened dysphagia.[15]

Transcervical cricopharyngeal myotomy is the traditional surgery used to treat cricopharyngeal dysfunction. Endoscopic laser myotomy has better outcomes and fewer complications[13] than the open procedure. However, altgough myotomy is effective at releasing the contraction of the upper esophageal sphincter, it does not treat the progressive degradation of the pharyngeal muscles. Severe dysphagia, choking, and aspiration pneumonia still occur in these patients, leading to the permanent use of a nasopharyngeal tube and a feeding jejunostomy, and, ultimately, to a tracheostomy.

As the mutated *PABPN1* protein with abnormally expanded alanine repeats is believed to be the key factor causing OPMD, a genetic approach targeting *PABPN1* at the transcript level was reported by Malerba et al.[2] DNA-directed RNA interference, delivered by adeno-associated virus vectors, was used to completely knockdown all endogenous PABPN1 and replace it with normal *PABPN1* that was resistant to that inhibition. The dual gene therapy was reported to be effective in the mouse model and in *ex vivo* human OPMD myoblasts. Because OPMD only involves specific skeletal muscles, it is more feasible to treat than other congenital muscular dystrophies. Gene therapy might be a novel treatment available to OPMD patients in the future.

4. Conclusion

Dysphagia is an important and potentially fatal symptom of OPMD. Underdiagnosis and a lack of awareness of OPMD may lead to choking, aspiration pneumonia, and death in multiple members in affected families. Currently, there is no definitive treatment for OPMD, but rehabilitation exercises and surgical intervention are helpful for relieving dysphagia.

Author contributions

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Writing – original draft: Andy Wei-Ge Chen.
Writing – review & editing: Shey-Lin Wu, Chieh-Sen Chuang, Mu-Kuan Chen, Chin-San Liu.

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