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(CASE REPORT)

Oculopharyngeal muscular dystrophy, rare genetic disorder: A case report

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Abstract

Oculopharyngeal muscular dystrophy (OPMD) is a rare genetic disease that targets the muscles of the eyelids and pharynx. OPMD is caused by an abnormal expansion of a trinucleotide repeat (GCG) in the coding region of poly-A binding protein nuclear 1 gene (PABPN-1). Patients with OPMD present mainly with ptosis, dysphagia, and extremity weakness. Herein, we present a case report of a patient with OPMD. Our case report will provide detailed information regarding the outpatient management of OPMD, as well as possible therapies of the future for these patients.

Keywords: Oculopharyngeal Muscular Dystrophy; Ptosis; Dysphagia; Outpatient Therapy

1. Introduction

Oculopharyngeal muscular dystrophy is a rare genetic disease that targets the muscles of the eyelids and pharynx. OPMD usually manifests in the age range of 40-60 years old, with patients that usually report a family history of the disease, along with presenting with symptoms of ptosis and dysphagia. Until today, treatment of OPMD has mainly been supportive as there is no cure for OPMD yet. Recent progress that has been targeting genetic expression has been showing promising results in developing a cure for OPMD.

2. Case Presentation

A 54-year-old female with a past medical history of hypothyroidism and hemochromatosis presented to our clinic complaining of a six month history of eye drooping and intermittent sensation of food getting stuck in her throat. Associated symptoms also included weakness in bilateral upper and lower extremities. Patient reported acute-onset of symptoms that started as mild but were gradually worsening. Patient denied any prior similar symptoms in the past. Patient also denies any recent travel, tick bite, recent upper respiratory tract infection or gastrointestinal illness.

Upon reviewing the patient's family history, the patient reported that she is French-Canadian. Father was deceased at age of 40 following a motor vehicle accident. Mother is healthy with no significant past medical history. Additionally, the patient reported that her grandfather had ptosis and dysphagia with onset 5 years prior to his death.

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Vital signs were as follows: body temperature, 37.0°C; blood pressure, 128/82 mm Hg; heart rate, 87 beats/min; respiratory rate, 17 breaths/min; and oxygen saturation, 98% on room air. Physical examination was significant for the following: Eyes: bilateral ptosis. Neck: supple, no lymphadenopathy. Musculoskeletal: normal motor strength, normal range of motion and no gait abnormalities.

Initial plans included obtaining a complete blood count (CBC), complete metabolic panel (CMP), thyroid stimulating hormone (TSH), folic acid level, vitamin B12 level and iron studies. Given patient's ethnicity, as well family history significant for similar symptoms, a blood test for polyadenylate-binding nuclear protein 1 gene (PABPN-1) was ordered as well. After labs were obtained, patient was instructed to follow up in two weeks.

On the following visit, the patient reported that her symptoms of ptosis, sensation of food getting stuck in her throat, and muscle weakness had continued worsening. At that visit vitals were found to be within normal limits. Physical examination showed similar findings and was unchanged from initial visit. CBC, CMP, TSH, folic acid, vitamin B12, and iron studies were within normal limits. However, an expanded number of DNA sequence (GCN) repeats was noted on the PABPN-1 gene which indicated mutation in the PABPN-1 gene, confirming the diagnosis of oculopharyngeal muscular dystrophy. The patient was provided education regarding her new diagnosis. Referrals to ear nose and throat (ENT) surgery, ophthalmology, and physical therapy were sent. Patient continued to be seen at our clinic monthly during which she was also following with an ENT surgeon, ophthalmologist, and physical therapist.

The patient presented to our clinic for a routine visit six months following her diagnosis and reported that she continued to suffer from sensation of choking with dry solid foods. Subsequently, she was referred to a nutritionist and has since been carefully consuming enough nutrition to maintain energy without weight loss. Decision was made between patient and ENT surgery to hold off on any procedures for the time being. In terms of eye drooping, patient underwent a blepharoplasty and reports that symptoms have greatly improved following and she denies any loss of vision or difficulty closing her eyelids. Lastly, patient reports she has been going to physical therapy three times a week with less feelings of weakness and improvement in her activities of daily life.

3. Discussion

Oculopharyngeal muscular dystrophy (OPMD) is a genetic condition that typically begins in adulthood. As its name suggests, OPMD is characterized by muscle weakness, primarily in the muscles of the eyelids causing ptosis, and weakness of the throat muscles causing dysphagia. Other manifestations as disease progresses can include tongue atrophy, chewing difficulties, facial muscle weakness, axial muscle weakness, and proximal limb girdle weakness (1). The prevalence of OPMD varies amongst different ethnic groups. Cases of OPMD have been reported in 29 countries (1). In the United States, only small case series have been reported and patients consisted of mainly French Canadian or Hispanic descent. (2,3,4). OPMD is most common among the French Canadian population, estimated to affect 1 in 1,000 individuals, and has been found to be even more common in the Bukaran Jewish population of Israel, affecting 1 in 700 people (1). Treatment approaches to patients with OPMD have mainly been supportive and target the symptoms of ptosis and dysphagia.

Given the patient's chief complaints, in addition to the patient's ethnicity and family history, her presentation warranted suspicion for OPMD and supported genetic work up. The patient's father likely suffered from OPMD as well, but given that he passed away at a young age, symptoms did not yet manifest. OPMD is an aggressive disease, therefore emotional and supportive care are an important part of management to implement. With this consideration, our patient was seen in our clinic more frequently, education and resources regarding her disease were provided, and it was made certain that our patient was following up with the other indicated specialties regularly. This special attention to management aided us in identifying the development of early signs of depression in our patient, enabling us to provide medications as well psychological support.

3.1. Current treatment for OPMD

As mentioned above, there is currently no cure for OPMD and the only treatment available is mainly supportive.

- Ptosis: Surgical treatment includes blepharoplasty by either resection of the levator palpebrae aponeurosis or frontal suspension of the eyelids (4).
- Dysphagia

Treatment has been approached as step up management. First, the patient will need referral to a nutritionist for dietary modifications in order to ensure enough caloric intake. If symptomatic dysphagia has a significant impact on a patient's

quality of life, then surgical intervention should be considered. The most common surgical approach to dysphagia in patients with OPMD is myotomy of the upper esophageal sphincter muscle (5). Myotomy of the upper esophageal sphincter muscle improves swallowing by relaxing the constriction of the upper esophageal sphincter muscle. However, this surgical approach will not prevent the eventual progressive degeneration of the pharyngeal muscles that result in an increased risk of aspiration and severe weight loss.

- Weakness of the upper and lower extremities: Patients will benefit from physical and occupational therapy.
- Surveillance

Routine surveillance of the patient's status is critical for patients with OPMD. Patients should be routinely examined for oculomotor involvement, and their nutritional status and diets should be evaluated as well. Patients with OPMD should also have their respiratory status monitored closely, given their increased risk for both aspiration and nocturnal hypoventilation.

3.2. Future therapeutic modalities for OPMD

OPMD is caused by abnormal expansion of a (GCG) trinucleotide repeat in the coding region of poly-A binding protein nuclear 1 (PABPN-1). The disease results from an alanine expansion in the N-terminal domain of the PABPN-1 gene. Therapeutic modalities have targeted protein aggregation, inhibiting transglutaminase, as well as halting the function of mutant PABPN-1 genes.

- Trehalose

An osmolyte which works as a chemical chaperone, allowing it to stabilize partially unfolded protein molecules, inhibiting protein aggregation (6). It has been shown to reduce aggregate formation and toxicity of mutant PABPN–1 gene in cells. In addition, oral administration of trehalose to OPMD transgenic mouse models has been shown to reduce muscle weakness and decrease aggregate formation.

- Cystamine

A trial was done that evaluated the efficacy of inhibiting transglutaminase in the treatment of mice with OPMD, given that mice with mutated PABPN-1 gene were noted to have an elevated amount of transglutaminase. Cystamine, which functions as a transglutaminase inhibitor, was given to mice with PABPN-1 gene mutation and demonstrated an improvement in mice gripping better with their paws, maneuver on a wire, and movement around the cage (7).

- Gene expression

Recent trials have been showing the benefit of using recombinant vectors in targeting treatment of OPMD. A Two recombinant AAV vectors were made of a recombinant AAV serotype 8, which produced a small inhibitory RNA to silence endogenous (mutant and wild-type) PABPN-1 and an AAV vector expressing a codon-optimized version of wild type PABPN-1 that took advantage of amino acid codon degeneracy to produce the wild-type PABPN-1 protein from a mRNA that is not targeted by the anti-PABPN-1 (8). A two-vector approach has shown improvement in the restoration of muscle strength to wild-type levels.

Since two-vector approach in humans is challenging given the increased technical risk and cost, a recent development of BB-301 which combines the essential elements of the two vectors into a single 'silence and replace' recombinant one AAV vector. The recombinant AAV vector approach has demonstrated full restoration of muscle strength and weight, as well reduction of fibrosis in mice models (9).

4. Conclusion

Oculopharyngeal muscular dystrophy is an autosomal dominant genetic disorder caused by an abnormal expansion of a trinucleotide repeat (GCG) in the PABPN-1 gene. OPMD is an aggressive disease that can cause dramatic physical and emotional symptoms. Patients with OPMD should be monitored closely and follow up with multiple specialists including a nutritionist, physical therapist, ophthalmologist and ENT surgeon. Given recent advancements, promise has been shown regarding the management of OPMD patients in the future.

Compliance with ethical standards

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Statement of ethical approval

Statement of informed consent has been provided.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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