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CASE REPORT

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Diplopia in a patient with Satoyoshi syndrome and mitochondrial myopathy

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ABSTRACT

We report on the case of a 42-year-old woman who presented with diplopia to the Strabismological Outpatient Clinic in 2017. The first manifestations of the condition – including blurred vision and diplopia of variable severity – occurred in 2006. The patient reported a history of asymptomatic retinal vasculitis in the left eye. On account of the woman's systemic manifestations, she had undergone a diagnostic work-up in the neurology, dermatology, and cardiology departments. Based on the clinical findings and the results of additional examinations, the patient was diagnosed with Satoyoshi syndrome and, in subsequent years, also with mitochondrial myopathy.

KEY WORDS: diplopia, Satoyoshi syndrome, mitochondrial myopathy.

INTRODUCTION

The diagnostic work-up in patients with ocular motility impairment requires taking a detailed history with a focus on both ophthalmic and systemic conditions. A complete ophthalmic and strabismological examination is necessary. In addition, patients with diplopia often need a referral for laboratory tests, imaging examinations, and consultations with other medical specialists. Both physicians referring patients to strabismology outpatient clinics and diplopic patients themselves may not link their ophthalmic abnormalities with systemic diseases. This case report serves to highlight that diplopia may be caused by rare disorders. The diagnostic process in diplopic patients must be oriented towards determining the cause of the condition and followed by the selection of an appropriate treatment modality. In most cases, effective treatment of the underlying disease or reducing the severity of symptoms can help the patient. The variable nature of the disorder with intermittent periods of more severe diplopia and remission usually indicate non-ophthalmic causes.

The aim of this article is to highlight the complex etiology of visual disorders based on a case report.

CASE REPORT

The patient, a 42-year-old woman, presented to the Strabismology Outpatient Clinic at the Infant Jesus Teaching Hospital in Warsaw in 2017. On admission, she complained of double vision and eye pain that had occurred periodically since 2006, and varied in severity. During the 6 months preceding the medical appointment, her condition had deteriorated. For a few years, because of a broad variety of symptoms, she underwent a diagnostic work-up for possible systemic connective tissue disorders (including systemic lupus erythematosus), multiple sclerosis, and cardiomyopathy. The woman did not see links between the reported ophthalmic manifestations and systemic diseases.

From the age of about 20, the patient had experienced dizziness, painful muscle spasms in the upper and lower limbs and in the paraspinal muscles, impaired exercise tolerance, increased fatigability of muscles staying in spasm for a longer period of time, involuntary movements of the limbs, pain in the fingers and toes worsening at night, pain in the sternocleidomastoid muscles and in the region of the sternocostal joints accompanied by a feeling of breathlessness. Furthermore, the patient experienced recurrent diarrhea and hematuria as well as menstrual disorders. As a child, she suffered multiple fractures of limb bones as a result of minor injuries which do not usually lead to such consequences in healthy people. Fractures occurring in patients with Satoyoshi syndrome are associ-

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ated with tendon and muscle spasms causing musculoskeletal instability. The patient denied any head injuries. In 2011, she developed alopecia. Since 2012, the patient has been under the care of the Dermatology Outpatient Clinic. Based on examinations conducted in the Department of Dermatology, the Department of Neurology, and the Department of Cardiology, the diagnoses of systemic lupus erythematosus, multiple sclerosis, and cardiomyopathy were excluded. Following a more extensive diagnostic work-up in the Department of Dermatology, in 2016 the patient was diagnosed with Satoyoshi syndrome, a rare autoimmune disease. Since the woman also presented with a range of complaints that are not specifically associated with Satoyoshi syndrome, a repeat neurological diagnostic work-up was performed, leading to the diagnosis of a genetic condition – mitochondrial myopathy.

The patient was under the care of ophthalmology outpatient clinics in other healthcare centers from 2006. A review of her medical files reveals the absence of eyebrows and eyelashes, normal position of the eyes in orbits, nystagmus of the right eye, and limitation of left eye abduction. In 2017, the patient was referred to the Strabismology Outpatient Clinic at the Department of Ophthalmology. During assessment, the following findings were made: convergent eye alignment (Figure 1), bilaterally impaired eye abduction, normal bilateral corrected visual acuity, and intraocular pressure of 16 mmHg in both eyes. On slit-lamp examination, the anterior segment in both eyes was normal. Hess-Lees screen test performed in the patient is shown in Figure 2.

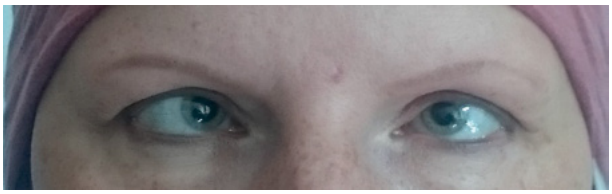

Figure 1. Convergent eye alignment

Ophthalmoscopic examination of the left fundus revealed sheaths around the temporal branch of the superior central retinal artery (Figure 3A). An occlusion of this vessel was suspected, which is why the diagnostic work-up was extended to include fluorescein angiography (FA). The examination showed normal flow through the vessel with the sheaths present, and no dye leakage that would indicate damage to the vascular wall (Figure 3B). FA assessment performed with Spectralis system using a 102° wide-angle lens found no abnormalities in the angiograms either in the posterior pole area or on the periphery of the retina (Figures 3C and 3D).

At present, the patient's systemic and ophthalmic complaints vary in severity, with periods of remission and exacerbation of symptoms. She receives chronic treatment with oral glucocorticosteroids at doses adjusted to the severity of complaints. Because of recurrent diarrhea and hematuria, the patient requires supplementation and continuous rehabilitation of the locomotor system. Currently, the woman's general condition is good. She is independent and does not require caregiver assistance. Unfortunately, hair regrowth on the scalp, eyebrows and eyelashes has not been achieved despite treatment. Based on five-year

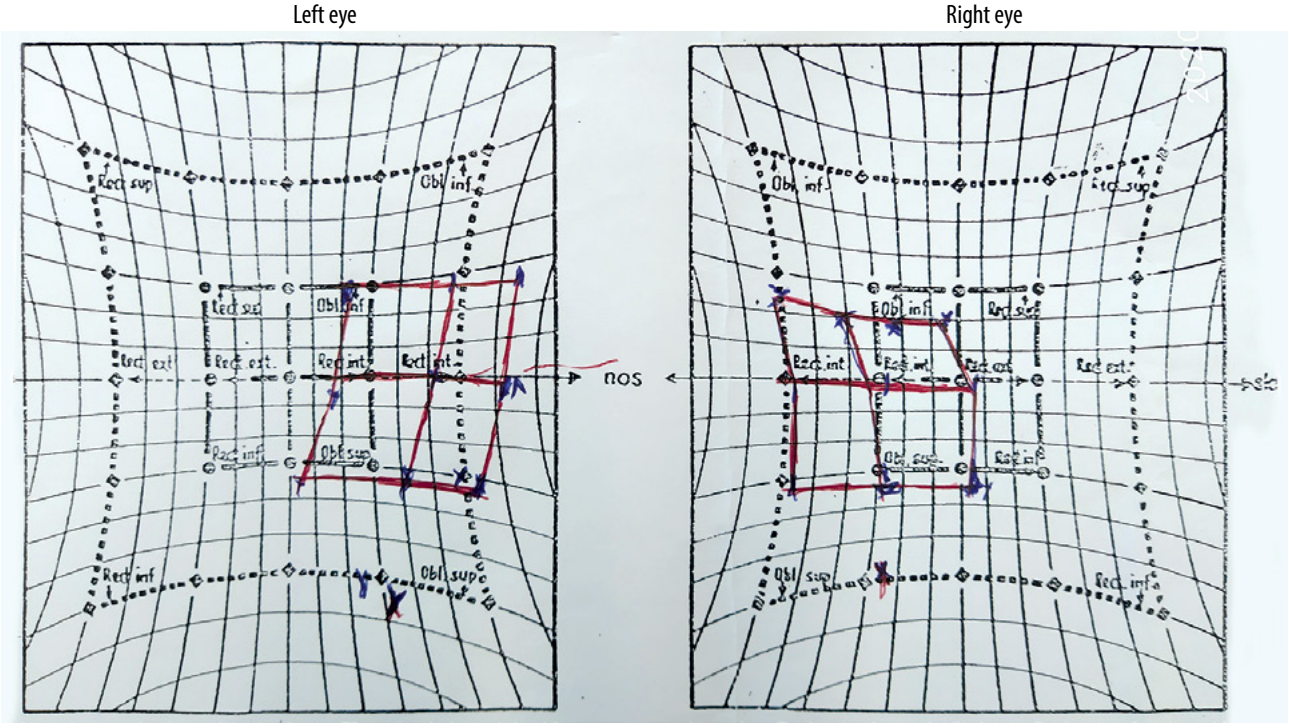

Figure 2. Hess-Lees screen test – convergent eye alignment

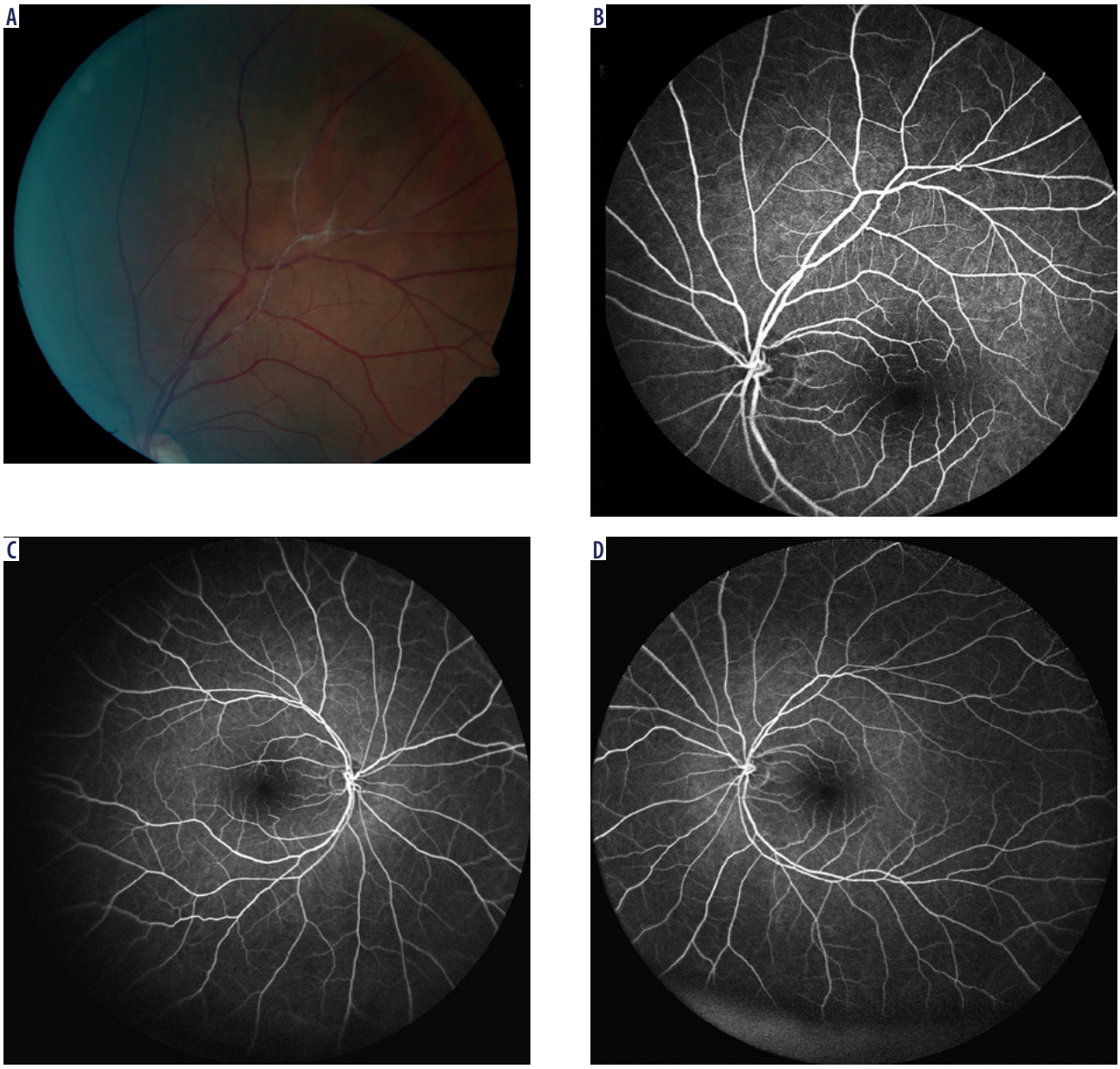

Figure 3. **A)** Color fundus photograph of the left eye showing sheaths on the superior temporal retinal artery. **B)** Fluorescein angiography of the assessed vessel – no signs of dye leakage, normal blood flow. **C)** Normal angiogram (102° lens) of the right eye. **D)** Normal angiogram (102° lens) of the left eye

follow-up, the patient's ophthalmic condition is characterized by alternating periods of exacerbation and remission of diplopia. The patient complains of constant double vision and difficulty when turning eyes in extreme directions. The angle of abduction over the 5-year follow-up period is shown in the tables I-IV.

At this time, the patient's ophthalmic examination shows convergent eye alignment, difficulty in abduction, involuntary eye movements occurring at extreme gaze (probably related to muscle fibrosis), and normal visual acuity. The patient's current eye motility impairment in nine directions of gaze is shown in Figure 4. The attempt to prescribe prismatic spectacles was unsuccessful. The patient did not accept the correction because of variable severity of ocular motility impairment. The woman does not present with any ophthalmic abnormalities other than those described above.

DISCUSSION

Patients with diplopia presenting to an ophthalmologist require taking a thorough history. Consideration should be given to the time of onset (sudden onset or progressive course), direction (horizontal, vertical, oblique diplopia), and pattern (constant, intermittent, time-of-day effect, direction in which it is most marked). Diplopia can be classified as monocular, binocular or physiological. In cases of monocular diplopia, the eyes are aligned correctly. Monocular diplopia is usually due to ophthalmic conditions such as astigmatism, keratoconus, corneal haze, dry eye, lens subluxation, incipient cataract, changes in the vitreous,

Table I. Synoptophore examination – eye alignment in 9 directions of gaze (2017)

?	ET + 5° R = L	?
ET + 5° R = L	ET + 5° R = L	ET + 5° R = L
?	?	?

Table II. Synoptophore examination – eye alignment in 9 directions of gaze (2018)

?	ET + 20° R = L	?
ET + 15° R = L	ET + 23° R = L	?
?	?	?

Table III. Synoptophore examination – eye alignment in 9 directions of gaze (2020)

?	ET + 20° R = L	?
ET + 18° R = L	ET + 20° R = L	ET + 10° R = L
?	?	?

Table IV. Synoptophore examination – eye alignment in 9 directions of gaze (2022)

?	ET + 12° R = L	?
ET + 7° P = L	ET + 10° R = L	ET + 7° R = L
?	ET + 10° R = L	?

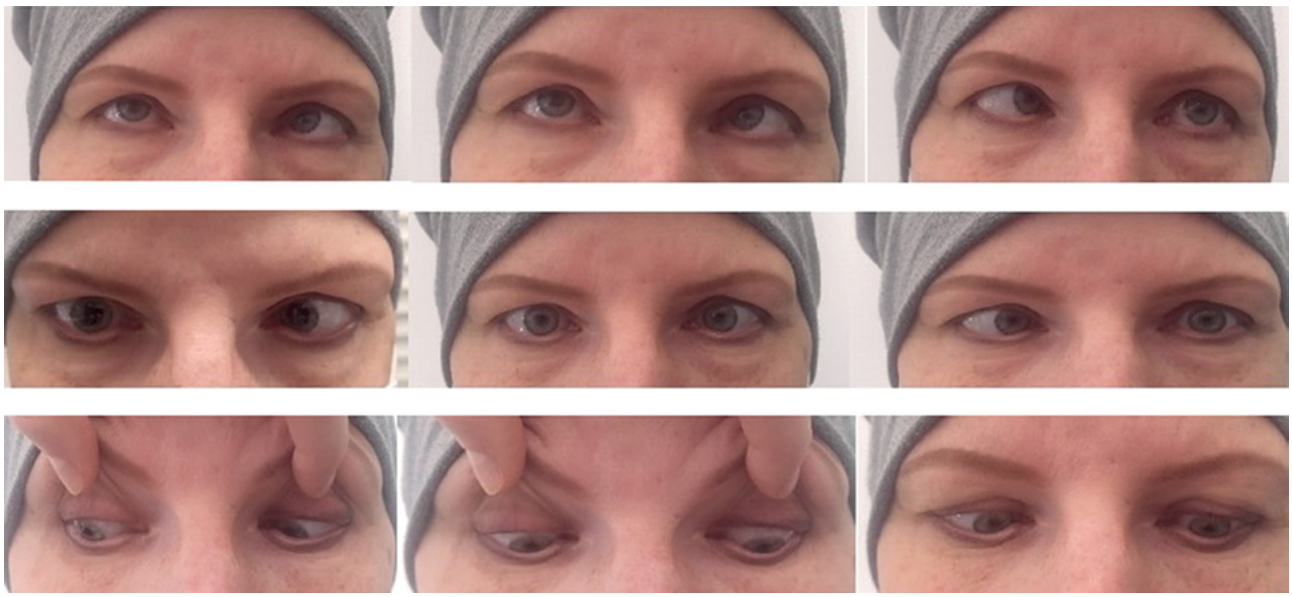

Figure 4. Patient's ocular motility in nine directions of gaze. Visible reduction in ocular motility in the temporal direction in both eyes

epiretinal membranes, or mental disorders. Binocular diplopia can be a manifestation of serious systemic diseases or decompensation of latent strabismus.

Satoyoshi syndrome is a very rare multiorgan disease described for the first time by Eijiro Satoyoshi and Kaneo Yamada in Japan in 1967 [1, 2]. The condition is also referred to as Komuragaeri disease (from the Japanese words "komura" meaning calf and "gaeri" meaning spasm) [2]. To date, more than 60 cases of Satoyoshi syndrome have been reported, mostly in Japan, India, the UK, Russia, and Argentina, as well as isolated cases in other countries [3, 4]. The diagnosis of Satoyoshi syndrome is challenging because the symptoms do not appear simultaneously. The first manifestations may occur in early childhood [2], but most commonly the onset is in the first or second decade of life. The syndrome is twice as common in women as in men. The average time from the onset of the first symptoms to the diagnosis is about five years, but there are reported cases where the diagnosis was made 30 years after the first symptoms appeared [3]. The underlying cause of the disease is most likely linked to autoimmune disorders [2-5]. Antinuclear antibodies (ANA) are detected in 60% of patients [3]. Comorbidity with other autoimmune diseases including myasthenia gravis, thyroiditis or thrombocytopenic purpura has been reported. There have been no familial cases of the disease, so a genetic background is unlikely. Diagnostic criteria presented by Rudnicka *et al.* [3] include one obligatory criterion – total or partial alopecia, and three additional criteria – intermittent painful muscle spasms, diarrhea, and positive antinuclear antibodies (ANA). Histological examinations – a skin biopsy specimen showing lymphocyte infiltration – are also included in the diagnostic assessment. Other pathologies, such as amenorrhea and skeletal abnormalities, are most likely secondary symptoms. Partial or complete alopecia with the loss of eyebrows and eyelashes occurs in all patients. Muscle spasms (intermittent, involuntary,

painful) were present in all patients described in the literature [3]. Spasms usually last from 30 seconds to a few minutes, and occur at a frequency of 5 to 15 times per day. Initially, they affect the lower limbs, but over time they become more severe and progress to involving the upper limbs, trunk, neck and facial muscles [3, 6]. Matsuura *et al.* were the first authors to describe abdominal muscle spasms as a manifestation of the disease [7]. Merello *et al.* and Matsumura *et al.* described cases of initial involvement of the masticatory muscles associated with impaired eating and speech disorders [8, 9]. Hegeri *et al.* described the case of a 14-year-old girl who first developed spasms affecting the small muscles of the hand, which then spread to the abdominal muscles, tongue, thigh muscles, and masticatory muscles [1].

Skeletal abnormalities affect approximately 66% of patients, the most common being short stature or joint deformities [3]. Diarrhea with carbohydrate intolerance occurs in 65% of patients, and endocrine disorders, mainly amenorrhea, have been reported in 50% of adult women [3]. Ishihara *et al.* described the case of a patient who developed sensory disturbances [10].

Satoyoshi syndrome should be differentiated from other diseases including Sjögren's syndrome, systemic lupus erythematosus, vitamin D-dependent rickets, adverse drug reactions, pituitary dwarfism, and juvenile idiopathic arthritis [3]. Sometimes patients are treated by a number of specialists separately because of the multitude of reported complaints and symptoms associated with the syndrome. The patient's physician in charge is a dermatologist, as the problem of hair loss usually prompts patients to seek advice from a dermatology specialist first. No publications addressing changes in the organ of vision have been found in the available literature.

In most cases, the first-line drug is prednisolone at a dose of 15-30 mg/day. Higher doses and intravenous infusions have also been used, though less commonly. The efficacy of treatment does not appear to be directly linked to the dose of glucocorticoids. A reduction in the severity of spasms and relief of diarrhea were achieved both at doses lower than 15 mg/day and higher than 30 mg/day. Reports of hair regrowth are rare, but in cases where it was achieved, the process took no less than 2-4 months of therapy. In addition to glucocorticosteroids, other reported therapies include intradermal triamcinolone injections and treatment with cyclosporine. In a single case, a good therapeutic outcome was achieved with immunoglobulins, but in other patients this treatment brought no improvement. In several patients, combination therapy with glucocorticosteroids, dantrolene sodium, diazepam or phenytoin was found to be effective [3].

Mitochondrial myopathies comprise a large heterogeneous group of disorders associated with primary dysfunction of the mitochondrial respiratory chain, manifesting as muscular diseases [11-13]. They may be caused by mutations of genes encoded in mitochondrial DNA (mtDNA) or of nuclear genes encoding mitochondrial components [12]. Mitochondrial myopathies are characterized by dysfunction of multiple systems and organs, wide variability in clinical presentation, and poor genotype-phenotype correlation. Mitochondrial disorders occur at a prevalence of 1 : 10,000, but the presence of mtDNA mutation is even more common, with a prevalence estimated at 1 : 200 [13]. Symptoms of mitochondrial diseases occur primarily in tissues abundant in mitochondria, where intensive metabolic changes take place, such as the muscles and the brain. Most mitochondrial myopathies occur before the age of 20, and often begin with exercise intolerance or muscle weakness [13]. Other symptoms include heart failure, cardiac arrhythmias, dementia, motor disorders, stroke-like episodes, deafness, impaired visual acuity, ptosis, limited eye movement [14, 15], vomiting, nausea, headache, dyspnea, and convulsions [12, 13]. The severity of symptoms varies depending on the type of myopathy. The most prevalent myopathies include Kearns-Sayre syndrome, MELAS syndrome (myopathy, encephalopathy, lactic acidosis and stroke-like episodes), MERRF syndrome (myoclonic epilepsy with ragged red fibers), CPEO syndrome (chronic progressive external ophthalmoplegia), and Pearson marrow pancreas syndrome. The diagnosis is made on the basis of histopathological examination of a muscle specimen, genetic tests, cerebrospinal fluid analysis, and echocardiography. There is currently no specific treatment for any of the mitochondrial myopathies [13]. Physical therapy can extend the range of muscle motion and improve the overall physical performance. Vitamin therapies based on riboflavin, coenzyme Q and carnitine have been noted to provide a subjective improvement by reducing fatigability and increasing the perceived energy levels in some patients [11, 13].

In the patient reported here, the severity of ophthalmic symptoms and the variable nature of the pathologies were related to the severity of underlying diseases. Treatment with higher doses of steroids reduced abnormalities in eye alignment and ocular motility.

CONCLUSIONS

Ocular symptoms may often be the earliest manifestation of a number of autoimmune, degenerative or proliferative conditions. The diagnosis of patients presenting with ocular motility impairment and diplopia requires thorough history-taking to determine the onset and progression of the complaints, and full ophthalmic and strabismological examinations. Often, the collaboration of multiple specialists as well as laboratory tests, and genetic and imaging assessments are required. Establishing the correct final diagnosis can be a prolonged and challenging process. Also, it needs to be noted that the diagnosis of one disease does not preclude the coexistence of other conditions. Further patient management and appropriate ophthalmic treatment can be selected once the underlying cause of diplopia is determined. Mitochondrial myopathy is one of the genetically conditioned diseases that may cause diplopia. There are no literature reports of impaired ocular motility in

patients with Satoyoshi syndrome, but the disorder characteristically presents with spasms of fine striated muscles, often including the muscles of the face.

DISCLOSURE

The authors declare no conflict of interest.

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