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Case Report

RECURRENT ATYPICAL OPTIC NEURITIS AS THE LEADING SIGN OF FABRY DISEASE

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SUMMARY – Acute optic neuritis has the age and sex adjusted incidence of 1-5/100,000 in general population. It is mostly a disorder affecting young Caucasian women (31-32 years). Patients present to a wide range of clinicians including general practitioner, emergency physician, ophthalmologist, neurologist, etc. There are two main clinical presentations of optic neuritis, typical and atypical. It is of great importance to distinguish these two types of optic neuritis in order to detect the underlying etiology and plan appropriate and timely treatment. We present a young female patient (36 years) admitted to Department of Ophthalmology due to visual loss on the left eye. Magnetic resonance imaging showed demyelinating lesions in frontal and parietal lobe, periventricularly, in mesencephalon and right cerebellar hemisphere, and left optic neuritis; magnetic resonance angiography was normal. The patient's history revealed renal dysfunction, hypothyroidism, and miscarriage in the 6th month of pregnancy due to eclampsia, and Fabry disease in family (mother and two sisters). She was transferred to the Department of Neurology for further evaluation of the demyelinating disorder of the central nervous system. The patient received corticosteroid therapy (methylprednisolone 1 g) for 5 days with regression of visual disturbances on the left eye. After this acute treatment, the question of definitive diagnosis remained, along with further treatment of the underlying cause. Considering renal dysfunction, miscarriage, arterial hypertension, positive genetic and biochemical testing for Fabry disease in close relatives (mother), we suspected that she also had Fabry disease. She was tested and the results were positive. We concluded that optic neuritis was the first sign of Fabry disease in this case, reflecting acute atypical neuroinflammatory disease.

Key words: *Optic neuritis; Fabry disease; Diagnosis; Therapeutics; Female; Case reports*

Introduction

Acute optic neuritis has the age and sex adjusted incidence of 1-5/100,000 in general population. It is mostly a disorder affecting young Caucasian women (31-32 years). Patients present to a wide range of clinicians including general practitioner, emergency physician, ophthalmologist, neurologist, etc. There are two main clinical presentations of optic neuritis, typical and atypical.

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In most patients with optic neuritis, the pathology is demyelination of the optic nerve, which may reflect symptoms of the clinically isolated syndrome suggestive of multiple sclerosis, or be one of the signs of multiple sclerosis if there is radiological or clinical evidence for brain lesions and clinical symptoms of dissemination in space and/or time according to revised McDonald criteria for multiple sclerosis. In these patients, prognosis is good and visual recovery is expected in 90%-95% of cases. This is a typical form of optic neuritis.

Atypical forms of optic neuritis exhibit 'red flags' for more aggressive etiology and do not recover without directed treatment. It is of great importance to dis-

tinguish these two types of optic neuritis in order to detect the underlying etiology and plan appropriate and timely treatment.

Fabry disease is an X-linked inherited lysosomal storage disease caused by mutations (or alterations) in the a-Gal A (*GLA*) gene, which result in insufficient activity of the a-Gal A enzyme. Lysosomes are primary digestive units within cells, therefore they are enriched with enzymes that break down or digest particular compounds and intracellular structures. Function of the GLA enzymes is to break down globotriaosylceramide (GL-3 or Gb3), lyso-GL-3/Gb3 and related glycolipids by removing terminal galactose sugar from the end of these glycolipid molecules. The enzyme deficiency causes continuous build-up of GL-3/Gb3 and related glycolipids in body cells, resulting in cell abnormalities and organ dysfunction[1-3]. In females, GLA enzyme activity levels depend not only on GLA mutations of the X chromosome, but also on the lyonization effect[4,5].

Fabry disease affects one *per* 40,000 to 60,000 males. This disorder also occurs in females, although the prevalence is unknown. Milder, late-onset forms of the disorder are probably more common than the classic, severe form. The average age at diagnosis is approximately 30 years. Delayed diagnosis may be due to the rarity of the disease and/or the nonspecific nature of its early symptoms[6,7].

Symptoms increase with age due to the progressive glycolipid accumulation in vascular system, kidneys, and heart, leading to kidney failure, heart disease or stroke. Involvement of the central nervous system (CNS) in Fabry patients is mainly due to cerebral vasculopathy affecting both small and large cerebral vessels. Macroangiopathy usually leads to ischemic stroke, whereas microangiopathy is usually the cause of progressive white matter lesions confirmed by magnetic resonance imaging (MRI) in about 80% of Fabry patients (both genders)[8,9].

Case Report

We present a young female patient (36 years) admitted to Department of Ophthalmology due to visual loss on the left eye (Figs. 1 and 2). MRI showed demyelinating lesions in frontal and parietal lobe, periventricularly, in mesencephalon and right cerebellar hemisphere with contrast enhancement (Figs. 3-6), and left optic neuritis (Figs. 7 and 8); magnetic resonance angiography was normal. The patient's history revealed renal dysfunction, hypothyroidism, miscarriage in the 6th month of pregnancy due to eclampsia and genetically confirmed Fabry disease in family (mother and 2 sisters). She was transferred to Department of Neurology for further neurological evaluation. Cerebrospinal fluid evaluation showed mild pleocytosis, normal blood brain barrier function and oligoclonal bands type 3. Visual evoked potentials indicated prechiasmal dysfunction of the left optic nerve. Octopus visual field showed normal finding on the right eye and decreased RF 10.0 and inferior altitudinal deficit within 60 degrees on the left eye. Genetic testing for Fabry disease was positive (two heterozygous mutations), with decreased alpha galactosidase activity values and increased Lyso GB3 values. Neurological examination showed loss of visual acuity on the left eye, without any other neurological signs and symptoms.

The patient received corticosteroid therapy (methylprednisolone 1 g) for 5 days with regression of visual disturbances on the left eye.

According to the radiological and laboratory findings, as well as clinical diagnosis, we concluded that the patient probably had Fabry disease with microangiopathy complications (autoinflammatory vasculopathy) of the brain white matter and therefore treatment with enzyme replacement therapy was introduced. She started enzyme replacement therapy in April 2016. After 7 months of therapy, she presented clinically again with loss of visual acuity of the left eye. Visual evoked potentials showed increased latency of the P100 waveform and N2 response bilaterally, more pronounced on the left eye. Fundus showed the beginning of vascular sclerosis. Octopus visual field of the right eye showed normal finding, left eye RF 11.1 and inferior altitudinal deficit within 60 degrees on the left eye. Optic nerve and retinal nerve fiber imaging showed a decrease of the average retinal nerve fiber layer (RNFL) thickness of the left eye (especially decrease of RNFL thickness in the temporal lower quadrant of the left eye), decrease of vertical thickness of the neuroretinal rim of the right eye, as well as decrease of the average C/D ratio of the right eye and vertical C/D ratio on both eyes. Follow up MRI of the brain and neck showed two new small punctiform lesions, one in the splenium of the corpus callosum on the left and one

VEP-Pattern

Protocol / Run	N75 ms	P100 ms	N145 ms	P100 µV	Size
VEP					
1.1 T5 - Cz	78,90	112,80	147,30	1,2	16
1.2 O1 - Cz	79,50	112,80	145,50	5,0	
1.3 Oz - Cz	79,80	116,10	146,40	7,2	
1.4 O2 - Cz	78,60	115,50	147,60	1,9	
1.5 T6 - Cz	78,60	113,70	147,60	0,41	
L - VEP					
1.1 T5 - Cz	93,60	130,80	161,70	0,44	16
1.2 O1 - Cz	93,60	129,00	162,60	3,2	
1.3 Oz - Cz	88,20	128,40	162,30	3,2	
1.4 O2 - Cz	86,40	128,40	162,00	0,35	
1.5 T6 - Cz	84,00	127,50	160,80	0,73	
R - VEP					
1.1 T5 - Cz	78,90	113,40	150,90	0,79	16
1.2 O1 - Cz	78,60	113,70	150,90	4,3	
1.3 Oz - Cz	78,00	113,70	150,90	6,5	
1.4 O2 - Cz	78,90	113,70	150,30	0,93	
1.5 T6 - Cz	78,00	114,60	150,90	1,1	

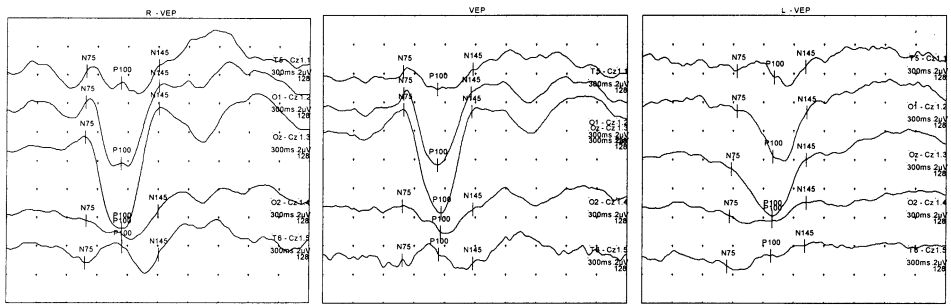

Fig. 1. Visual evoked potential pattern after 7 months.

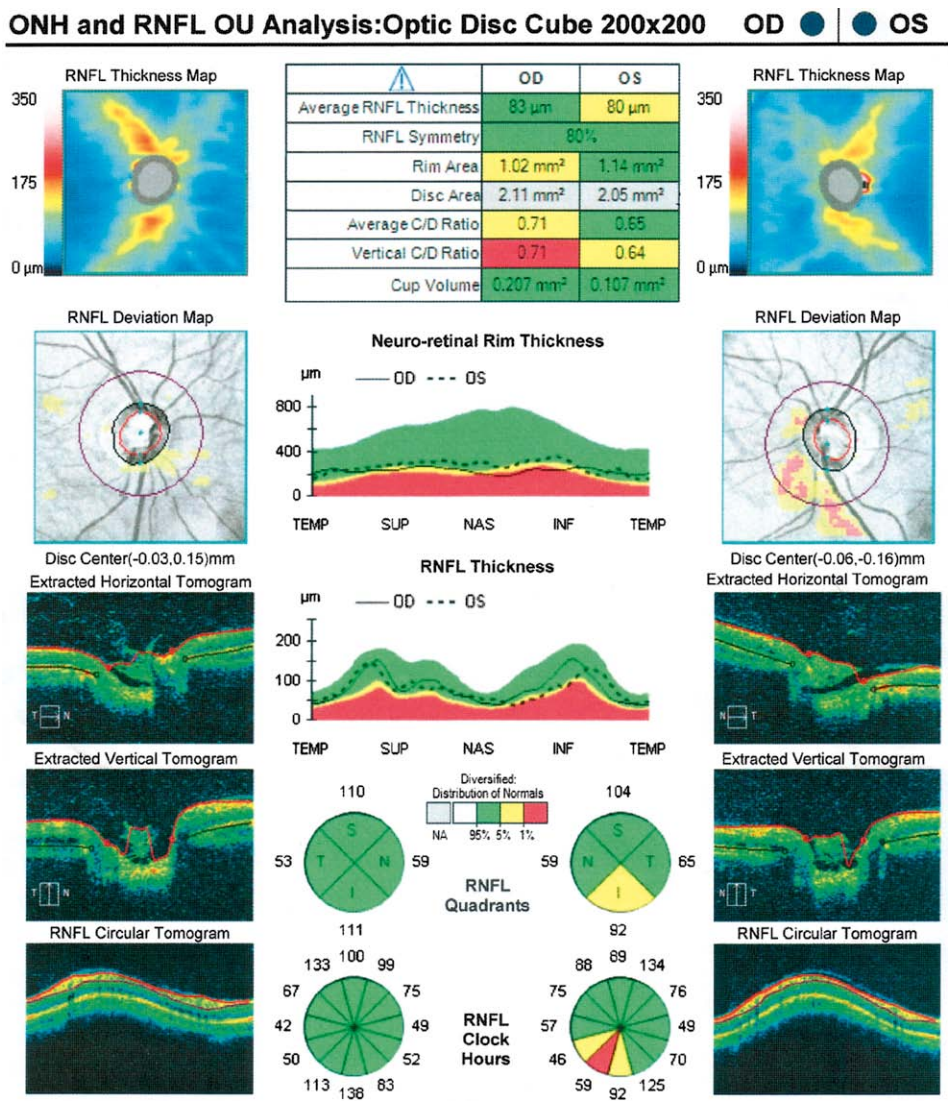

Fig. 2. Optic nerve and retinal nerve fiber imaging after 7 months.

subcortically in the left frontal lobe (Figs. 4 and 6) and optic neuritis of the left eye (Fig. 8). There was no contrast enhancement of parenchymal lesions. The patient received corticosteroid therapy (methylprednisolone 1 g) for 5 days with regression of visual disturbances on the left eye.

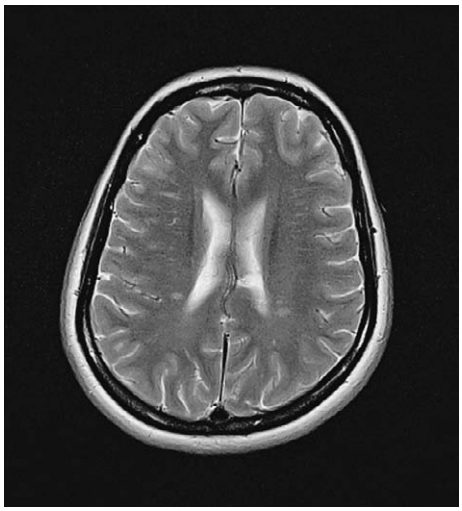

Fig. 3. Horizontal T2 MRI section: multiple demyelinating lesions.

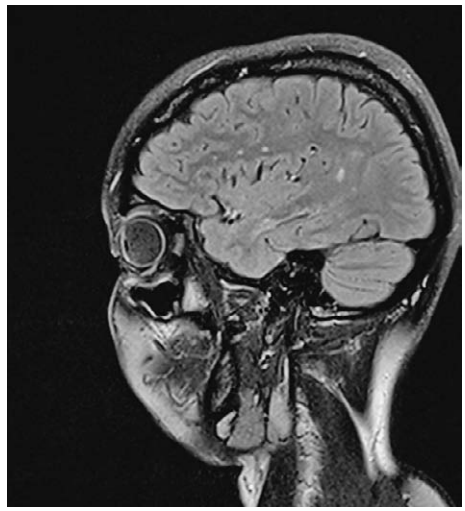

Fig. 5. Sagittal T1 MRI section: multiple demyelinating lesions.

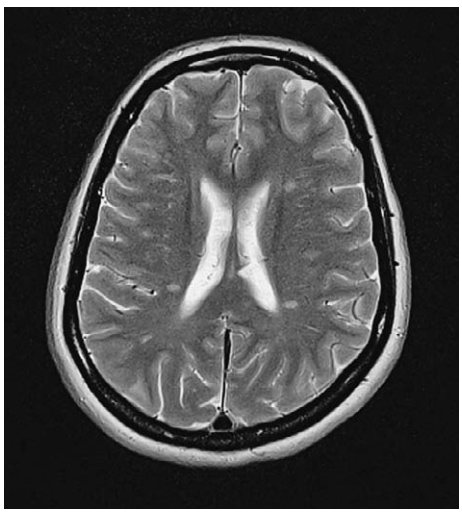

Fig. 4. Horizontal T2 MRI section after 7 months: multiple demyelinating lesions.

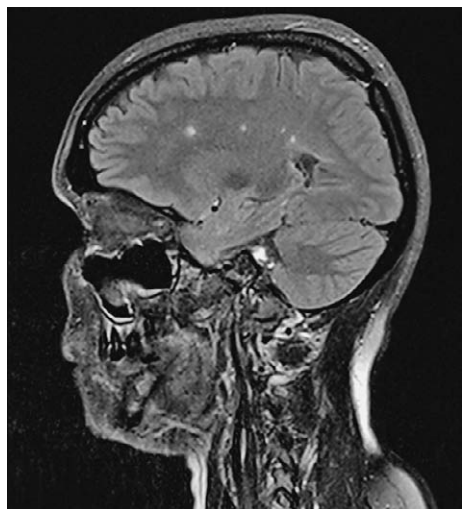

Fig. 6. Sagittal T1 MRI section after 7 months: multiple demyelinating lesions.

Discussion

Fabry disease affects young people and can develop monosymptomatic courses, which only involve CNS without any medical history of other classic Fabry symptoms such as angiokeratoma, cornea veriticillata, or heart and kidney disease. In such cases, atypical optic neuritis can be the first and only sign of the disease. It is of great importance to distinguish whether it is typical optic neuritis as part of multiple sclerosis or atypical optic neuritis as a sign of some other etiology. Differential diagnosis of optic neuritis requires detailed workup to exclude any other inflammatory or non-inflammatory brain white matter diseases, optic nerve compression, hereditary diseases (Leber's hereditary optic neuropathy), nutritional or toxic maculopathies, inflammatory or granulomatous causes anti aQ4, anti MOG, sarcoidosis, systemic lupus erythematosus, human immunodeficiency virus, syphilis, Lyme disease, Bartonella, tuberculosis, Behçet's syndrome, paraneoplastic retinopathy, chronic relapsing inflammatory optic neuritis, storage disorders (Fabry disease), etc.

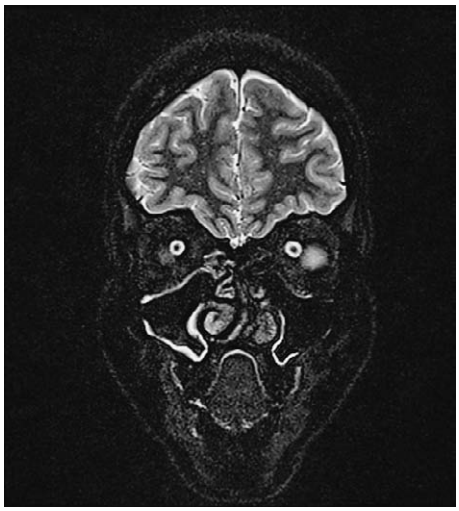

Fig. 7. Coronal T2 MRI: optic neuritis of the left eye.

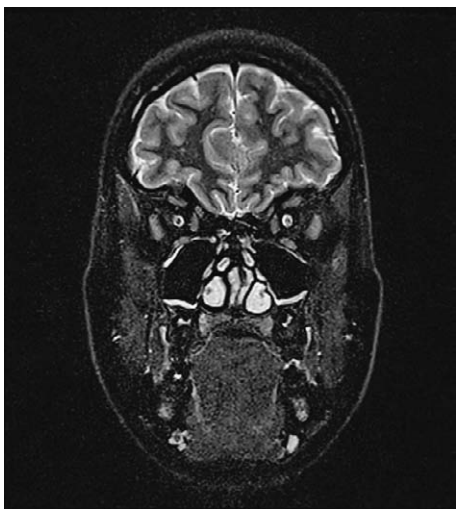

Fig. 8. Coronal T2 MRI after 7 months: optic neuritis of the left eye.

Usually, MRI of the cervical spinal cord is not performed in Fabry patients, and lesions at these locations are probably underestimated. In most cases, there are no white matter lesions in the spinal cord in Fabry patients, which can be one of the distinguishing parameters, but their presence does not exclude the disease; in cases of optic neuritis, data on the presence of such lesions can give additional information in differential diagnostic workup[9].

Cerebrospinal fluid changes are also present in Fabry patients and are defined as 'aseptic meningitis' or chronic meningitis with mild to moderate pleocytosis (76 cells/μL) and slightly elevated total protein levels (up to 800 mg/L) suggesting disturbed blood brain barrier function, mostly with lympho-monocytic response. Results of postmortem studies showed high accumulation of ceramide trihexoside in choroid plexus and leptomeninges in Fabry patients. These findings suggest an aseptic inflammatory process triggered by the stored lipids acting as foreign body stimulus. Oligoclonal bands can also be positive in cerebrospinal fluid of Fabry patients, they have high sensitivity in multiple sclerosis patients, but also are highly unspecific and can occur even after unspecific infections. On the other hand, in patients with optic neuritis as the only clinical sign of the disease and positive oligoclonal bands, it is hard to distinguish if it is typical optic neuritis as part of multiple sclerosis or atypical optic neuritis as a sign of some other central nervous system disorder[10,11].

Good differential diagnosis in the early stages of optic neuritis is of great importance for planning long-term treatment which will cure symptoms and underlying condition and prevent organ damage and disabilities. In Fabry patients, enzyme replacement therapy has shown good results in disease control. In optic neuritis, corticosteroids are the treatment of choice in acute phase of the disease. In atypical forms of optic neuritis caused by Fabry disease, it is of great importance to introduce corticosteroid treatment in the acute phase of optic neuritis and to plan long-term enzyme replacement therapy in order to minimize underlying vascular and changes of choroid plexus and leptomeninges due to Gb3 deposits. A combination of these treatments will reduce the number of optic neuritis relapses, as well as RNFL (axonal loss) and consecutive visual disturbances. In the follow up of optic neuritis patients, MRI of the head and neck with contrast, visual evoked potentials, visual field, and Optical Coherence Tomography Provider Network Operations (OCT PNO) should be performed in order to evaluate activity of the disease, and its morphological and functional presentation.

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Sažetak

PONAVLJAJUĆI ATIPIČNI OPTIČKI NEURITIS KAO PRVI ZNAK FABRYJEVE BOLESTI

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Fabryjeva bolest je rijetka X vezana lizosomska bolest nakupljanja koja zahvaća više organskih sustava u organizmu, a u središnjem živčanom sustavu (SŽS) se prezentira kao lezije bijele tvari koje su posljedica vaskulopatije i autoimunih procesa na razini koroidnog pleksusa. Prikazuje se slučaj mlade žene (36 godina) koja je primljena na našu Kliniku zbog poremećaja vida na lijevom oku. Nalaz magnetske rezonance (MR) mozga je pokazao demijelinizacijske lezije u frontalnom i parijetalnom režnju, periventrikularno, u mezencefalonu, desnoj hemisferi malog mozga te optički neuritis lijevo. Nalaz MR angiografije mozga je bio uredan. U osobnoj anamnezi se doznaje da se bolesnica liječila zbog bubrežne insuficijencije, hipotireoze te da je u 6. mjesecu trudnoće imala spontani pobačaj uslijed eklampsije. U obiteljskoj anamnezi se doznaje da majka boluje od Fabryjeve bolesti. U analizi cerebrospinalnog likvora nađe se blaga pleocitoza, uredna funkcija krvnomoždane barijere te sinteza IgG unutar SŽS-a, oligoklonske vrpce tip 3. Vidni evocirani potencijali pokazali su disfunkciju prekjazmalno lijevo. Genetsko testiranje na Fabryjevu bolest pokazalo je pozitivan nalaz, 2 heterozigotne mutacije, smanjenu aktivnost alfa galaktosidaze te povišene vrijednosti Lyso GB3. Bolesnica je primila pulsnu kortikosteroidnu terapiju (metilprednisolon 1 g) kroz 5 dana na što dolazi do regresije smetnji vida na lijevom oku. Nakon akutnog liječenja simptoma postavlja se pitanje konačne dijagnoze i dugoročnog liječenja. Uzimajući u obzir prisutnost bubrežne insuficijencije, eklampsiju u trudnoći uz spontani pobačaj, pozitivne rezultate genetskog testiranja i biokemijskih analiza za Fabryjevu bolest te nalaza MR mozga koji opisuje promjene dominantno u području stražnje cirkulacije, zaključili smo da će se u bolesnice najvjerojatnije raditi o Fabryjevoj bolesti uz autoimune promjene u SŽS-u i da je bolesnicu potrebno liječiti enzimskom nadomjesnom terapijom. S obzirom na smetnje vida i nalaze pozitivnih oligoklonskih vrpci koji mogu govoriti i u prilog multiple skleroze potrebno je dalje pratiti bolesnicu klinički i neuroradiološki kako bi se postavila definitivna dijagnoza.

Ključne riječi: *Optički neuritis; Fabryjeva bolest; Dijagnostika; Terapijski postupci; Ženska osoba; Prikazi slučaja*