Published in final edited form as:

J Neuroophthalmol. 2012 March ; 32(1): 23–26. doi:10.1097/WNO.0b013e318230feab.

Clinical Neuro-ophthalmic Findings in Familial Dysautonomia

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Abstract

Objective—To define the clinical neuro-ophthalmic abnormalities of patients with familial dysautonomia (FD).

Methods—Sixteen patients (32 eyes) with the clinical and molecular diagnosis of FD underwent thorough neuro-ophthalmic clinical evaluation.

Results—Visual acuity ranged from 0.05 to 1.0 decimal units and was reduced in 15 of the 16 patients. Mild to moderate corneal opacities were found in most patients but were visually significant in only two eyes. Red-green color vision was impaired in almost all cases. Depression of the central visual fields was present on automated visual fields in all patients, even in those with normal visual acuity. Temporal optic nerve pallor was present in all cases and was associated with retinal nerve fiber layer loss in the papillomacular region. Various ocular motility abnormalities also were observed.

Conclusions—Patients with FD have a specific type of optic neuropathy with predominant loss of papillomacular nerve fibers, a pattern similar to other hereditary optic neuropathies caused by mutations either in nuclear or mitochondrial DNA affecting mitochondrial protein function. Defects of eye movements, particularly saccades, also appears to be a feature of patients with FD.

Keywords

familial dysautonomia; hereditary optic neuropathy; Riley Day syndrome

Introduction

Familial dysautonomia (FD), also known as the Riley-Day syndrome or hereditary sensory and autonomic neuropathy type III, is an autosomal recessive disorder that impairs the

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development of specific sensory and autonomic neurons during embryogenesis (1-6). The most common mutation, located on the long arm of chromosome 9 (9q31) (7-8), results in a splicing abnormality and a deficiency of the I κ B kinase complex-associated protein (IKAP or Elp 1) (9-13). The splicing abnormality is tissue-specific: neurons produce mostly mutant IKAP mRNA and little protein product, while other cells produce both normal and mutant mRNA in different ratios (14). IKAP is widely expressed throughout the body, with its expression being highest in neural tissue and the retina (15).

Patients with FD have a complex neurological phenotype with decreased pain and temperature perception, impaired sense of taste, abnormal swallowing, gait ataxia, decreased/absent myotatic reflexes, and extremely labile blood pressure. Vision deteriorates with age in patients with FD, and by adulthood most patients have severe visual loss (16-19). Visual impairment has dramatic consequences for these patients as they lack proprioceptive afference and thus rely heavily on vision for activities of daily living. Dry eye secondary to lacrimal deficiency, myopia, corneal anesthesia, corneal abrasions and ulcerations were believed to be the main cause of visual deterioration (16,18). However, based on clinical observations, the degree of visual impairment cannot be explained by corneal complications alone, and visual loss occurs in patients without severe corneal damage. Early case reports describe exotropia, pupillary dysfunction and optic nerve atrophy, but it is not known whether these neuro-ophthalmic features occur in all patients (19-25). Our aim was to define the neuro-ophthalmic phenotype of patients with FD.

Methods and Materials

Subjects

We evaluated 32 eyes in 16 patients with FD, 6 males and 10 females with a mean age of 26.8 years (range 12-61). All patients had typical clinical features and the diagnosis was confirmed by genetic testing. All patients signed an informed consent and the NYU Institutional Review Board (IRB) approved the study.

Methods

Best-corrected visual acuity (BCVA) was assessed independently for each eye using Snellen optotypes with optimum refractive correction, and the results were presented as decimal units. Color vision was estimated using Ishihara plates (Ishihara 16 plates, Tokyo, Japan), and Hardy-Rand-Rittler color vision test (American Optics, Richmond, USA). Pupillary reflexes were assessed using a standard bright light (Halogen illuminator lamp HPX™ 3.5 V, Welch Allyn, NY, USA). Ductions, fixation, saccades, pursuit, convergence, vestibulo-ocular reflexes and optokinetic responses were assessed. Visual fields were obtained using a Humphrey Field Analyzer (HFA 750i Carl Zeiss, Dublin, CA, USA), with the 30-2 program and SITA Fast strategy using optimal refractive correction. Anterior segments were examined by slit lamp bio-microscopy. Ocular fundus examination was performed with a binocular indirect ophthalmoscopy (Keeler Vantage, London, UK) and slit lamp bio-microscopy (Haag Streit BQ 900, Koeniz, Switzerland) to evaluate the posterior pole using a noncontact lens of + 78 diopters and red free light with particular attention of the retinal

nerve fiber layer. In some patients, mydriatic color and red-free fundus photos (TRC 50 IX, Topcon, Tokyo, Japan) were acquired.

Results

The main neuro-ophthalmic findings are summarized in Table 1. Myopic refractive defects were present in 27/32 eyes. Most patients had a history of corneal lesions. We classified the corneal opacities as absent or mild (17 eyes), moderate (13 eyes) and severe (2 eyes). In none of the eyes was the opacity severe enough to preclude fundus examination through indirect ophthalmoscopy or non-contact lens bio-microscopy, even in the two severely affected eyes. Band keratopathy was present in one eye.

BCVA ranged from 0.05 to 1.0 decimal units. Most of the patients had acuity below 0.5, which did not appear to be due to corneal opacities or other surface abnormalities except in two eyes.

A red-green color vision defect was found bilaterally in all patients examined with variable degrees of severity and in four eyes of two patients, blue-yellow color deficiency also was detected.

Central or cecocentral visual field defects were predominant and found in 26 eyes. Four eyes had generalized, deep field depression, and this was associated with poor visual acuity (Table 1). Two eyes had normal visual fields.

Retinal nerve fiber layer loss was detected in all eyes, accompanied by temporal pallor of the optic disc. Twenty-five eyes showed only pallor in the temporal region of the optic nerve together with a wedge shaped loss of fibers in the papillo-macular bundle (Table 1). In 7 eyes there was also generalized optic nerve pallor, but this was always more evident in the temporal portion of the disc (Fig 1). Retinal vascular tortuosity was present in 6 eyes.

Ocular motility was impaired in various ways (Table 1). While ductions and versions were full in all patients, exophoria was seen in almost all cases (30 eyes). This was associated with limited convergence. There were no limitations of excursions. Saccades tended to be dysmetric; more often they were hypermetric with corrective refixation saccades. In some cases there was adduction slowing which was confirmed by testing with the optokinetic drum. Pursuit movements were interrupted by repeated saccadic intrusions in almost all cases.

Discussion

The main neuro-ophthalmic finding in patients with FD was a characteristic optic neuropathy. Visual acuity was reduced in most patients and appeared to be worse in the older patients. Corneal opacities were present in many eyes, but, in almost all eyes, the central corneas appeared clear enough by slit lamp bio-microscopy to allow for good vision. The predominant red-green color deficiency that was almost always detected is consistent with optic neuropathy, although some blue color deficits in some eyes may suggest additional retinal dysfunction. The central and cecocentral visual field defects seen in most patients are

very similar to those seen in patients with hereditary, toxic and nutritional deficiency optic neuropathies. In some cases, the central and cecocentral visual field defects were profound and associated with poor visual acuity and color perception. Also, in almost all cases there was optic nerve head pallor, which was confined to or most prominent in the temporal portion of the optic nerve head and associated with a wedge shaped area of retinal nerve fiber loss in the papillomacular bundle.

The abnormalities in ocular motility suggest that the disease process in FD can affect ocular motor control mechanisms. The dysmetric saccades, saccadic intrusions and disrupted pursuit eye movements that we observed might indicate loss of the fine-tuning control of eye movements. Whether these defects are due to abnormalities at the level of the extraocular muscle or due to a supranuclear control deficit cannot be determined by our studies.

There were few retinal findings in our patients. The macular area was always normal with no pigment epithelial changes. In some patients, the fundi showed myopic changes associated with myopic refractive errors greater than -7.00 diopters. Retinal vascular tortuosity was seen in 8 eyes, as previously reported (17,22).

Few authors have described optic neuropathy in FD patients. Rizzo et al (20) studied three patients with FD and found optic neuropathy, which they believed was “a rare manifestation of this rare disease”. They did suspect that it appeared later in the lives of affected patients (20). Diamond et al (21) described a group of FD patients who had abnormal visual evoked potentials and optic nerve pallor. Other case reports describing the optic neuropathy in patients with FD have also been published without additional details (22-25). We detected optic nerve damage in all patients, some as young as 11 years old and all with loss of retinal nerve fibers in the papillo-macular bundle.

Involvement of central visual field, deficient color perception and the temporal optic disc pallor that we have observed in patients with FD, is strikingly similar to the findings in other hereditary optic neuropathies such as Leber's hereditary optic neuropathy (LHON), dominant optic atrophy (DOA) and some recessive optic neuropathies. These optic neuropathies all have in common mitochondrial protein dysfunction caused by mutations either in nuclear or mitochondrial DNA (26,27). This suggests that the primary mutation in FD may affect mitochondrial proteins synthesis in the nervous system.

Acknowledgments

Study funding: Supported in part by the Dysautonomia Foundation, Inc., National Institutes of Health (U54-NS065736-01), The Massachusetts Lions Clubs/Research to Prevent Blindness Challenge Grant and Carl Zeiss Meditec.

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Fig 1.
Fundus appearance of a patient with FD demonstrating bilateral temporal optic disc pallor and loss of the retinal nerve fiber layer in the papillomacular bundle.

Table 1

Neuro-ophthalmic findings in patients with FD.

Subjects	n		
Age			
0-20	7		
20-40	6		
40-	3	16	patients
Corneal Opacities			
Absent or Mild	17		
Moderate	13		
Severe	2	32	Eyes
Visual Acuity ¹			
0.6 - 1.0	2		
0.25 - 0.5	19		
0.05 – 0.2	11	32	eyes
Color Vision ²			
15/15-11/15	6		
10/15-6/15	14		
5/15-1/15	12	32	eyes
Visual Field Loss			
Mild / Non specific	2		
Generalized Depression	4		
Central-Cecocentral	26	32	eyes
Pupillary Reflex			
Normal	4		
Hiporeflexive	28		
Arreflexive	0	32	eyes
Optic Nerve			
Normal	0		
Temporal Pallor	25		
Temp + Diffuse Pallor	7	32	eyes
Ocular Motility			
Exophoria	30		
Saccadic Dysmetria	18		
Saccadic Intrusion	24		

¹Decimal notation²Ishihara Color plates (Tokyo, Japan)