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Case Report

Ophthalmology Section

Riley-Day Syndrome in a Hispanic Infant of Non-Jewish Ashkenazi Descent

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ABSTRACT

Riley-Day syndrome is an autosomal recessive sensory and autonomic neuropathy. Patients present a lack of fungiform papilla, alacrima and usually feeding difficulties. It is present almost exclusively in Ashkenazi Jewish individuals and has a poor prognosis. We describe an unusual case of Riley-Day syndrome with pseudostrabismus in a non-Ashkenazi Jewish patient. A one-year-old female infant was referred for evaluation of strabismus, absence of fungiform papillae, feeding difficulty, gastroesophageal reflux and episodes of self-mutilation. Deep tendon reflexes were depressed, the blinking rate and corneal reflex were diminished as well and corneas were opaque due to corneal erosions. Reduced lacrimal production was confirmed by the Schirmer test. Eye drops were recommended every 2-3 hours for corneal erosion and the patient was referred to the genetics department for further diagnostic confirmation.

Keywords: Dysautonomia, Familial, Hereditary-sensory and autonomic neuropathy type III

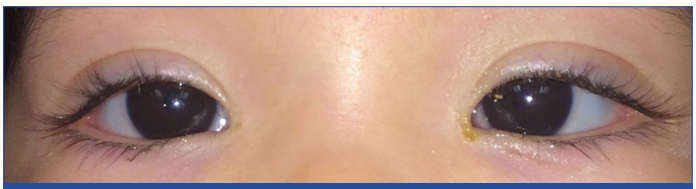
CASE REPORT

A one-year-old female infant was referred to the ophthalmology department for strabismus evaluation [Table/Fig-1]. The patient was born from a full-term pregnancy without complications during birth or any known disease; birth weight was 2530 gm. Family history was unremarkable.

The parents were non consanguineous and did not have Ashkenazi Jewish ancestry. At the age of two months, she began with feeding difficulty and poor sucking reflex. Gastroesophageal reflux resistant to usual management was diagnosed. Two months later, she was ablactated because of premature teeth eruption. Her mother noticed that every time the patient was fed, facial erythema and drooling occurred. Due to a suspicion of an allergic disorder, intradermal-reactions were carried out, which were negative, including histamine. In order to rule out an allergic disorder, intradermal-reactions were conducted. Nonetheless, all reactions (including histamine) were negative.

The patient also started with episodes of self-mutilation: she bit her lips and tongue, which left permanent scars [Table/Fig-2]. No crying or facies of pain were expressed during these episodes.

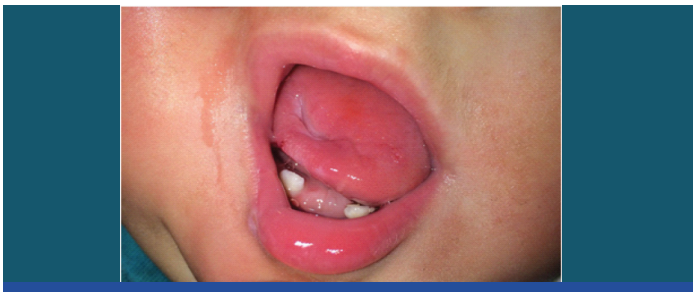
On neurological evaluation, depressed deep tendon reflexes without muscle atrophy were found. Seizures were discarded by a normal electroencephalogram. Other important medical conditions were episodes of prolonged fever with temperatures of up to 40°C (104°F) lasting for about 15 days with a poor response to acetaminophen. Due to oropharyngeal breathing, nebulization was recommended by her paediatrician. A diminished blinking rate and opaque corneas were also noted. At the ophthalmology clinic, she presented with generalized hypotonia, delayed motor development, depressed deep tendon reflexes, global analgesia, scars and absence of fungiform papillae on the tongue and bilateral corneal erosions.



[Table/Fig-1]: Pseudostrabismus with opaque corneas.

Corneal sensitivity was tested by moving a wisp of cotton from the limbus towards the center of the cornea while monitoring for a blink reflex. This was absent in both eyes. Diminished lacrimal production was confirmed by the Schirmer test, with this being reduced with and without topical anesthesia (6 mm in the right eye and 5 mm in the left eye after 5 min). Pupillary hypersensitivity to pilocarpine was also found. Miosis was induced after approximately 20 minutes following topical administration of pilocarpine 0.0625%. Based on clinical manifestations and signs, a diagnosis of Familial Dysautonomia (FD) was made.

Eye drops every two to three hours were recommended for corneal erosions, which healed within two weeks of treatment. The patient was referred to the genetics department for further diagnostic confirmation. Minor haplotype 2 mutation was identified; which is the second most frequent mutation found on FD in Ashkenazi-Jewish descents.



[Table/Fig-2]: Tongue scar and drooling.

DISCUSSION

Hereditary Sensory and Autonomic Neuropathies (HSAN) are rare autosomal recessive disorders characterized by sensory and varying degrees of autonomic dysfunction [1,2]. A classification of four distinct forms of HSAN has been proposed by Dyck P and Ohta M [3]. Each variety is caused by different gene errors that affect different areas of small fiber neurodevelopment, which lead to variable phenotypic expressions [4]. HSAN type III or Riley-Day syndrome is the most common of these disorders. It presents at birth as a progressive disease and is almost exclusive to individuals with Ashkenazi-Jewish ancestry. Individual carrier frequency in Ashkenazi Jews is about 1 in 30 with an incidence of 1 per 3600 live births; non-Jewish individual frequency is unknown [1]. There is no specific

treatment for FD and its prognosis is poor. Management is focused on prevention of ophthalmologic and systemic complications. This case illustrates two unusual manifestations in a patient with FD. Firstly, her chief complaint was strabismus, an unusual initial manifestation of FD, although pseudostrabismus [Table/Fig-1] was diagnosed because of an epicanthal fold. Secondly and most significant, our patient had no Jewish ancestry.

The diagnosis of FD is based on clinical identification of sensory and autonomic disorders. The presence of alacrima, absence of fungiform papillae, depressed patellar reflexes, abnormal histamine test and at least one parent with Ashkenazi Jewish ancestry are usually sufficient to make the diagnosis [1-3]. Nevertheless, there are at least six reports in the literature of suspected FD in non-Jewish patients [5,6]. In 1993 the gene mutation causative of this disorder was found on the long arm of chromosome 9 (9q31) and in 2001, the gene was replicated [1]. A single point mutation was identified on the IKBKAP gene and more than 99% of affected individuals are homozygous for this common mutation [1]. In 2003, Leyne et al. described the first non-Jewish mutation in FD [6].

This mutation is of particular significance because it allows identification of FD in non-Jewish ethnicities and makes uncertain the role of this "cardinal" diagnostic criterion, as in our particular case. One patient, heterozygous for this common mutation and who inherited the missense mutation from a non-Jewish parent has also been described [5]. FD should not be ruled out if a patient meets all the "cardinal" criteria with the exception of Jewish ancestry.

Clinical expression and disease progression varies widely from individual to individual [Table/Fig-3]. Autonomic manifestations are prominent, involving peripheral and central tracts. Although alacrima is a cardinal feature of FD, it may not be immediately recognized since the overflow of tears is normal until about six to seven months of age [1,7]. Regarding the normal values for the Schirmer test for patients under one year of age are not established, our patient presented diminished values required for the diagnosis of FD. The earliest sign of autonomic dysfunction usually is feeding difficulties, gastroesophageal reflux and misdirection of the bolus, which causes recurrent aspiration pneumonia that can eventually result in chronic lung disease, a finding well-matched in our patient [2,6,7]. Sensory abnormalities in individuals with FD are uncommon and self-mutilation is rare. Pain and temperature perception are decreased but not absent. Da Silva et al., reported a case of a non-Jewish patient with FD who had self-harm episodes with bites on her lips, tongue and hands, which left permanent scars; burn scars on her trunk and limbs were also noted [8]. Similar scars were found in our patient's lips and tongue; self-teeth extraction was also documented, although burn scars were not present.

System Involved	Clinical Manifestations
Sensory System	Insensitivity to pain Abnormal temperature perception. Depressed patellar reflexes.
Autonomic System	Oropharyngeal incoordination. Esophageal dysmotility, gastroesophageal reflux. Insensitivity to hypercapnea and hypoxia. Breath holding. Orthostatic hypotension without compensatory tachycardia. Supine hypertension.
Motor System	Hypotonia. Mild to moderate developmental delay. Broad-based or mildly ataxic gait. Spinal curvature.
Cranial Nerves	Absence of overflow tears. Depressed corneal reflexes. Optic nerve atrophy. Strabismus. Deficient taste, especially sweet. Dysarthric, nasal speech.
Intelligence/Personality	Usually normal intelligence. Concrete or literal thinking. Skin picking. Resistance to change.

[Table/Fig-3]: Clinical manifestations of FD [2].

Cautious assessment of the other clinical signs and symptoms is necessary in order to distinguish between these disorders. Because there can be great variability in manifestations, clinical criteria are not always sufficient, so DNA molecular diagnosis, if available, might be performed to provide a definitive diagnosis.

CONCLUSION

Early diagnosis of FD is usually rare and difficult since many of the symptoms may be mild or nonspecific with diagnostic criteria appearing only later in life. Excluding Ashkenazi Jewish ancestry, our patient presented with all the "cardinal" criteria for the diagnosis of FD. Evidence supports the existence of gene mutations in patients with no Jewish family history. Our case shows that FD should not be excluded as a diagnosis if a patient fulfills all clinical and laboratory manifestations except for Jewish family history. Prompt diagnosis is essential to avoid further ophthalmologic and systemic complications. Bilateral corneal erosions, repeated aspiration pneumonia and self-mutilating scars, should always bring to mind the diagnosis of FD.

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