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Clinical diagnostic pearls in Familial Dysautonomia

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ABSTRACT

Rare genetic disorders are usually a diagnostic challenge mainly due to the complexity of the clinical presentation which is frequently changing with age and progression of the particular disorder. Familial Dysautonomia is a rare and complex multisystem disorder with peculiar but distinct clinical features . Some of those features are unique to this particular syndrome and the one who is familiar with them can quite easily reach the diagnosis without the need for sophisticated laboratory work-up. In this short review those "clinical pearls" will be described in some detail.

Familial Dysautonomia

Introduction

Familial Dysautnomia (FD, OMIM 223900) is an autosomal recessive rare and unique form of Hereditary Sensory and Autonomic Neuropathy type 3 (HSAN3), known by many as the eponym Riely –Day Syndrome. FD is caused by a mutated ELP1 gene formerly known as IKBKAP.

Lumping rare syndromes into groups of diseases rather than using either a descriptive name or an eponym for such disorders seems logical and even useful. However, keeping terms such as familial dysautonomia or for example hereditary insensitivity to pain with anhidrosis (HSAN 4), can be of immediate benefit to the clinician who gets a "snapshot view" of the symptomatic characteristics of the particular syndrome.

FD is indeed a rare and orphan disease by all accepted definitions[1].

Similar to other rare disorders, the number of publications describing features, mechanisms and genetics of such syndromes is disproportional to its rarity, thus, adding just another review of FD seems superfluous. Nevertheless, describing some "diagnostic pearls" which may be useful for those who have never seen a patient with FD, seems a good reason for "another review ".

FD is rare worldwide but is more common among Ashkenazi Jews (AJ). The incidence of FD live births in AJ living in North America was reported in 1970 as 1:10000[2] while in Israel it was 1; 3700 between the years 1977-1981[3]. The carrier rate among AJ when both parents were of Polish decent was 1:32, while it was 1:56 when only one parent was of Polish decent and 1:99 when both parent were of non- Polish decent. Moreover, if the parents were descendants of jews who used to live for centuries in the western part of the former Russian Empire situated between the Baltic and Black sea which today includes Poland, Lithuania, Ukraine and Belarus , the carrier rate increased to 1:18[4] .

The localization of the IKBKAP (ELP1) gene responsible for FD to chromosome 9 by Blumnefeld al. in 1993[5], and the identification of the founder mutation in this gene[6,7], allowed not only a precise diagnosis but also provided population at risk screening and prenatal diagnosis. Indeed, as for 2017, the carrier rate of FD among AJ in Israel is 1:25 (Shochat M, personal communication). At present, there are 110 living patients registered in the Israeli Dysautonomia Foundation (personal communication), however, we are aware of additional non-registered patients.

Inspite of the giant step forward which has been made in the detection of new cases, prenatal diagnosis and in few instances preimplantation diagnosis in affected families[8], those important discoveries did not change the grim prognosis of the disease although it led to a significant decrease of new patients and expanded our understanding of the pathophysiology of the disease.

As in other rare disorders with no cure, carrier detection as well as early diagnosis is essential and dependent on increased awareness and rapid, precise and simple diagnostic ques which I call "clinical pearls".

Familial Dysautonomia Clinical Pearls

There are very few multisystem diseases which present a uniform clinical picture with distinct and easily observed signs. FD stands out because to detect those signs one needs just a reflex hammer, a simple magnifying glass, a strip for Schirmer test, and a dropper for sweet, sour, salty and pepper solutions.

Even in extensive reviews such as the recently published work by Norcliffe-Kaufmann *et al*. which provides detailed clinical descriptions of FD[9], those "pearls" are frequently missed or just briefly noted.

Tongue Fungiform Papillae

FD is the only disorder in which the tongue fungiform papillae (FP) and to a lesser extent the circumvallate papillae and the accompanying taste buds are absent or markedly degenerated at birth[10-12]. Even if the tongue of the affected newborn appears normal to the naked eye, the magnifying glass will disclose flattened FP which are usually concentrated at the anterior surface and the tip of the protruded tongue. During infancy and childhood, the surface of the tongue appears smooth without the small red dots at the "summit" of the bulging FP. One can cause the papillae to stand out for better visibility by applying a few drops of lemon juice on the surface of the normal tongue and that of the affected new born and the difference in appearance will be more striking. It is not rare to find during childhood and adulthood large ulcerations due to repeated biting of the tongue accompanied by missing teeth which were self-extracted by the children. Both are the result of oro-dental self- mutilation[13]. When in doubt, we have used the ophthalmologic slit lamp which clearly showed either complete lack of FP or few remaining degenerated papillae. In contrast, numerous filiform papillae are present reminding the observer of a cotton field[11]. In mildly affected children the diagnosis may be missed since few FP can be seen. However, when the surface of the tongue is magnified, the few remaining FP appear flattened and degenerated[14]. The appearance of the tongue together with severe muscle hypotonia, absent or very sluggish tendon reflexes and swallowing difficulties in an infant born to one or both parents of AJ extraction, is highly suggestive of FD. Although many of those signs can be seen in newborns with a variety of hereditary and acquired disorders, the lack or paucity of tongue fungiform papillae at birth is unique.

Dysautonomic Face

Even at birth but often somewhat later during infancy and childhood, a peculiar characteristic facial appearance is noted. This characteristic facial appearance was first mentioned by Reily in his original description of the syndrome[15] and later by Moses[10] and McKendrik[16]. Rotem[17], was the first to coin the term "Dyautonomic face". In our study of Israeli patients with FD[10,] we have found a marked resemblance of facial appearance in 20/23 patients. The face and the upper lip were thin, frequently asymmetric, pale greyish with hypertelorism and divergent strabismus. The presence of a retrognathic mandible with steep plane angle and more horizontal growth axis contribute to this facial outstanding appearance[18]. The facial expression was frequently "frozen" and apprehensive, with an empty look and minimal grimacing. This facial expression is present in both children and adults.

Crying without Tears

Defective lacrimation**,** another cardinal sign of FD, was already mentioned in the original report by Riley[15]. Somewhat later, Dunnnigton gave an excellent description of this striking phenomenon, reviewed previously published cases with "congenital alacrima "which differed from FD, and was the first to examine pathologically the lacrimal glands and to note that those are entirely normal[19]. Recently, Mendoza-Santiesteban *et al*.[20] have elegantly (but partially) resolved the enigma of lack of tearing with normal functional glands and preserved efferent parasympathetic innervation. They have found that in spite of the ongoing degeneration of the corneal afferents causing insensitivity to touch and pain, remnants of basal tearing is still present in response to topical cholinergic agonists such as pilocarpine .Nevertheless , they were unable to solve the enigma of the lack of emotional tearing.

The combination of a dry and insensitive cornea results in corneal ulceration and keratopathy. We have found corneal ulcers in 12 out of 23 patients who were younger

than 19 years of age (15 younger than 10 years of age) [10]. Even with the best protective efforts to shield the eyes using a variety of devices, more than a quarter of the patients will progress to severe visual loss. Another important cause of visual loss in FD is the presence of progressive optic neuropathy due to loss of pappilomacular nerve fibers[21].

Sensory Impairment

When one is assessing the sensory impairment in FD the expected common clinical pattern of "glove and stocking anesthesia ", the hallmark of sensory neuropathy is replaced by rather peculiar response of the examined child. When a piece of cotton is applied to the skin to assess light touch, the child will immediately recoil expressing severe pain verbally or by gestures. At the same time, the child will be extremely ticklish when the skin of the chest or abdomen is gently stroked. Pediatricians tend to stroke their patient's hair as a sign of fondness but when they try to stroke the hair of a child with FD, he will immediately move his head away looking frightfully at the approaching hand. The experienced parent or pediatrician knows to avoid touching the hair which is perceived as extremely painful by the child. Evidently, combing the hair in the morning turns to be "mission impossible". Thus, this pattern of distorted pain perception rather than hypoesthesia or anesthesia common to many sensory neuropathies, can be coined dysesthesia. As already mentioned, severe self-mutilation in the form of forceful repeated pulling his/ her teeth leading to traumatic teeth extraction and tongue, lip and nail biting are not only damaging but also disfiguring and frequently lead to wound infection and even osteomyelitis [13, 22].

A helpful bedside test is the intradermal injection of 0.1 ml. of histamine sulfate which is often abnormal in FD[11]. Normal subjects experience immediate intense pain at the site of the injection, followed by a wheal and flare (the classical axonal triple response of Luis[23]), while in FD , local pain is diminished, while the "axonal flare " is very narrow. We have replaced this test by making a small vertical scratch on the volar surface of the forearm and observed the classical "triple response" in normals and lack of flare in FD and some other sensory neuropathies .

Taste

The lack of taste buds is associated with a peculiar taste abnormality which affects selectively the sweet perception accompanied by markedly decreased threshold for sour and salt[12]. Inexperienced parents believe that their child has a particular craving for sweet because he/she asks for many teaspoons of sugar to be put in his beverage.The truth of the matter is that their child needs a large amount of sugar to feel sweetness due to markedly decrease in the ability to taste sweet .On the other hand , they report that just a touch of lemon juice will be perceived as extremely sour . Indeed, we could corroborate those observations in our study which showed that the taste thresholds were the highest for sweet and the lowest for sour[12]. Using graded concentrations of sucrose, salt, pepper and lemon juice can be easily done at the bedside by applying drops of the particular test solution on the tongue and asking the school age child to point to the correct taste from a list of taste modalities. In younger children, the examiner can just watch the facial expression of the child while given the particular solution. He will easily identify the facial expression of acceptance when sugar is tasted and aversion when salt or bitter is perceived. Those reflex facial expressions are universal and were noted even in anencephalic newborns[24].

Interestingly, those selective taste modality impairment can be compared with the peculiar selective sensory perception described above.

In summary, for the clinical diagnosis of FD, it is best to let the parents or caregivers describe how their child perceives the described above sensory modalities and utilize the mentioned "Clinical pearls". Both of those will greatly facilitate the diagnostic work-up without the need for more sophisticated diagnostic tools.

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Conflict of Interest

None

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