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From Behr Syndrome to 3-Methyl-Glutacoinc Aciduria Type 3. An "Accidental" Diagnosis of a Case and a Mini-Review

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Abstract

In 1989, we have reported 19 patients with clinical features resembling Behr's syndrome. Somewhat later we were able to pin-point the metabolic nature of the disorder which became known as 3-methyl-glutaconic –aciduria type 3 or Costeff syndrome. The clinical features of this autosomal recessive disorder are quite unique with early onset visual impairment due to progressive optic atrophy, spasticity, cerebellar dysfunction and mental slowness resembling the clinical characteristics of Behr Syndrome (OMIM 21000); Since then, about 40 patients were published until 2020. The diagnosis of this very rare disorder which can be ameliorated with dietary supplements is quite simple to those who are familiar with the syndrome. Increasing the awareness of the syndrome by publishing new cases is quite evident. In this report we will describe in some detail the clinical features of a 25-year-old male who claimed compensation for worsening sight after a mild traumatic head injury. Following a court nomination of an expert neurologist (the author of this paper), the correct diagnosis was quite easily reached. The long road from Behr Syndrome to the establishment of a distinct disease entity and short literature review will be provided.

Keywords: Organic aciduria, infantile optic atrophy, 3-Methyl -Glutaconic Acid, Cerebellum, Cerebral palsy, Blindness.

Introduction

Carl Behr was a German ophthalmologist credited for the description of Behr's pupil (a wide and non-reactive pupil associated with field defect due to traumatic injury of the contralateral optic tract) in 1924 (Behr, 1924). In 1909 he reported a new hereditary syndrome consisting of optic atrophy, cerebellar ataxia, spasticity, mental deficiency and impaired bladder control, later given the eponym "Behr Syndrome" (Behr, 1909). The reported family consisted of 6 affected children in whom the presenting clinical signs were deteriorating vision starting during infancy and early childhood. The syndrome did not gain sufficient interest since its description was published in German. The syndrome was mentioned briefly in the main neurology and ophthalmology textbooks. A brief literature search disclosed 2 publications in French (Van Leeuwen & van Bogaert, 1942), and German (Kayser, 1955), mentioning the eponym "Behr Syndrome". Five additional papers were published between the years 1972-1984 (Dunn & Dolman., 1972; Henkes et al., 1972; Landrigan et al., 1973; Horoupian et al., 1979; Thomas et al., 1984). In 1988, I was asked to see a young girl which was followed at a pediatric neuro-rehabilitation center for slow motor development and deteriorating vision. The diagnosis of Behr syndrome was offered due to the presence of progressive optic atrophy, ataxia and spasticity with symmetrical hyperreflexia and bilateral Babinski sign. Two sisters had visual problems and were subsequently diagnosed. The healthy Jewish parents were first cousins, born in Bagdad, Iraq, who fled to Israel in 1947. Subsequently, 15 additional patients were detected who were followed at the same center as well as at a nearby ophthalmology department for "cerebral palsy", cerebellar degeneration and or optic atrophy. The patients belonged to 10 families, in 9 of them, both parents originated also from Bagdad (Iraq). Those data indicated an autosomal recessive inheritance.

From a syndrome to a new metabolic aciduria: The evolvement from Behr syndrome to 3-Methl-Glutaconic Aciduria type -3

Somewhat later, when screening for urinary organic acids became available and recognized as a helpful test for metabolic disorders, we have sent urine samples of our 3 female patients with Behr syndrome to Dr. O. Elpeleg, at the metabolic Unit, Shaare Zedek Medical Center, Jerusalem. We were quite surprised to find out that in all samples a significant increased

concentration of 3-Methyl-Glutaconic-Acid (3-MGA) was found. This unexpected finding was confirmed by repeated analysis of the original samples and additional samples from all our patients (Elpeleg et al., 1994). A significant progress step was the work of Nystuen, who used DNA samples from one of our Iraqi patients and found linkage to 19q13.2-q13.3 (Nystuen et al., 1997). The final step in establishing the genetic nature of our patients was the finding of introinic G-C mutation in the OPA3 gene (Anikster et al., 2001).

3-Methyl -Glutacoinic-Aciduria type -3, in brief

The largest group of patients with type 3-MGA was reported by Yahalom (Yahalom et al., 2014). This group of 28 patients, the majority of Iraqi origin, belonged to 21 families. Parental consanguinity was present in nine families. The age range of the patients was quite wide (6 months to 68 years). In all 17 patients where urine samples were available, 3-Methylglutaconic aciduria was detected. A known splicing mutation in the OPA3 gene (c1431G>C) was present in 14 patients while in the remaining patients the results of genetic studies were either unknown or have not been performed.

The clinical findings were somewhat variable due to the wide age range and disease duration, however, very early delayed developmental milestones and visual impairment due to optic atrophy were the main presenting symptoms. Cerebellar ataxia, spasticity and impaired stance and ambulation appeared somewhat later. Progression with age is very slow as patients in their fifties can still walk with assistant. Significant mental impairment and bladder control problems mentioned by Behr, were not encountered. Optic atrophy and reduced visual acuity are the main neuro-ophthalmology finding while on neuroimaging cerebellar atrophy is quite prominent. Life expectancy seems to be preserved. The rarity of the disease is responsible for misdiagnosis and significant diagnostic delay (Straussberg et al., 1998).

The scope of 3-Methyl-Glutaconic -Acidurias (3-MGA)

A variety of conditions are associated with MGA indicating that this abnormal finding is not disease specific but justifies a search for a metabolic disorder, especially mitochondrial defect. Indeed, Wortmann have found that among 227 urine samples with 3-MGA, 61 suffered from "classical" metabolic disorder, mainly fatty acid oxidation disorder and glycogen storage disease. The non- metabolic disorder group of 43 patients consisted mainly of neuromuscular and genetic/ chromosomal abnormalities. Twenty –three patients suffered from inborn errors of 3-MGA metabolism and in this group only one patient was diagnosed with 3-Methyl-Glutaconic -Aciduria. The majority of the remaining 51 patients suffered from mitochondrial disorders while fewer suffered from hypoglycemia (Wortmann et al., 2013). Those results confirm the ratify of 3-MGA type 3 which seems to be a unique rare genetic syndrome confined mainly to Jewish - Iraqi ancestry.

An "accidental" diagnosis of 3-MGA type 3

As quite often happens with rare syndromes, "once you have seen one, you have seen all". A few months after publication of our seminal paper describing 19 patients with clinical features of Behr Syndrome (Costeff et al., 1989), I have been nominated by the district court of Tel-Aviv, Israel, to serve as a court appointed neurologist in a case of a 25 year old man who was involved in a motor vehicle accident claiming compensation from the insurance company due to deteriorated vision which according to him occurred following the accident. He was accompanied by a friend and used a white cane which is used by blind people. His neuro-examination disclosed reduced visual acuity, optic atrophy, ataxia of gait, dysarthria, intentional tremor, symmetrical hyperreflexia, ankle clonus and bilateral Babinski sign. His parents were first cousins who were forced to leave Iraq in 1947. During the accident he sustained minor head trauma without features of traumatic brain injury. The person who came with him to the clinic reported that he was single, homeless and known for many years by the nick name "the shaky blind". Being allowed by the court to perform additional tests, he was found to have 3-GMA, with cerebellar atrophy on computed brain imaging. Genetic testing was refused.

Conclusion

There is a long way (and a bit of luck) from the identification of what seems to be a new clinical presentation before a definite phenotypic and genetic-metabolic disease entity is reached as was described hereby. The fact that the original description of the syndrome was in German can partially explain the paucity of publications of Behr syndrome between 1909-1972. The establishment of such a diagnosis is an important step in increasing the awareness of this rare disorder and enables precise genetic counselling and hopefully, treatment.

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