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"Mais-Nadim-Nasser Triad", A Useful Marker for Leukodystrophies Diagnosis

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Abstract

Background: Primary Hypotonia is a challenging diagnostic issue for pediatricians. Gray and white matter disorders are its main causes; the former, the neuronal storage diseases, have specific characteristics which make them relatively easy to diagnose. The latter, subject of this article, also called leukoencephalopathy, or leukodystrophy, has a wide spectrum of clinical features common with other brain diseases, but does not have any pathognomonic clinical sign, which makes it difficult to diagnose. Our mission is to label the most frequent combination of major characteristics of leukodystophies arising from injury to two or more brain associated organs, and have, at the same time, a high degree of specificity to these disorders, sufficient to put the diagnosis within our reach.

Methods: To achieve this, we reviewed the available literature about the majority of white matter disorders and examined the correlation between their main clinical features, to those of a group of leukodystrophic infants, of whom we report three out of thirteen cases.

Results: All thirteen infants, homozygous for the same mutation, showed three identical clinical and laboratory features which prevailed in most of the various types of leukodtrophy: namely; A- Marked truncal hypotonia, expressed by uncontrolled gravitational droppings of head and head lag, B- Uncontrolled eye movements; nystagmus, C- Abnormal brainstem evoked response audiometry.

Conclusions: The conjoined three major characteristics compose a novel triad that we named "Mais-Nadim-Nasser Triad"; an applicable marker in algorithms of the differential diagnosis of truncal hypotonia, nystagmus or sensory-neural deafness in childhood.

Keywords: Leuko-Encephalo-Pathies; Truncal hypotonia; Head-lag; Nystagmus; Brainstem evoked response audio-metry; Mais-Nadim-Nasser Triad

Abbreviations: HMLEP: hypo-myelination leuko-Encephalo-pathy; LD: Leuko-dystrophy; LDs: Leuko-dystrophies; MNN Triad; "Mais-Nadim-Nasser; PMD: Peliazeus-Mertzbacher Disease; BERA: Brainstem evoked response audiometry

Introduction

The differential diagnosis of infants presenting with primary truncal muscle weakness -as opposed to the peripheral hypotonia- is a broad medical issue [1-4].

The most common reasons for trunk hypotonia are destruction of the brain gray matter or the white matter. The former, is mainly due to neuronal degenerative storage disorders [2-14], which are clinically presented by some pathognomonic signs, but have a normal Brainstem Evoked Response Audio-Metry (BERA test). However, the white matter myelin production disorders, the subject of this article, named as leukodystrophies (LDs), or Hypo-Myelination Leuko-Encephalopathies (HMLEPs) [14-19], ranging from the X-linked recessive Pelizaeus-Mertzbacher Disease (PMD) [20-22], which is the prototype of these disorders, through the autosomal recessive Mitchap-Sixty disease which was detected in 2009, etcetera [1,5-7,12,17], do not have a definitive diagnostic characteristic; instead they have a broad spectrum of non-specific markers [9].

The myelin defects lead to the loss of nerves conduction, causing truncal hypotonia which is expressed by lack of control on head stability, head lag and head "titubation"; a swinging head motion. The hearing function is also gradually lost, affecting social reactivity of the patient (Tables 1 and 2). The eye movements lose the ability to be controlled, eventually vision is lost. The other less frequent or "minor" signs are: irritability [9], failure to thrive, loss of the social interest, absence of smile, decay of muscular tone, impossible swallowing, spastic paraplegia of limbs and epilepsy.

The fact that the above important features are non-specific for the LDs, necessitates, for their differential diagnosis, the use of expensive and time consuming diagnostic procedures such as computerized tomography, Magnetic resonance imaging MRI, and relatively less expensive tests such as Brainstem Evoked Response Audiometry BERA test which shows a lack of conduction of signals at the level of brainstem, Muscle Biopsy and Visual Evoked Response VEP test, so on. Our purpose is to label a common and useful clinical marker for easier diagnosis of the LDs, which will be dedicated for primary care physicians.

Methods

In this study, we hope to make sure that the symptoms and signs, which were mentioned above, are those prevailing in our group of children with LD, and that, according to medical literature available, they are identical to the symptoms and signs prevailing in most of the disorders of LDs, and thus create a joint clinical tool that makes LD diagnosis at hand.

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Abnormal features	Number of cases	%
Severe truncal muscle hypotonia #	13	100
Cherry red spot §	0	0
Cataract	0	0
Retinal pigmentation	0	0
Convulsions	6	46
Excessive ticklish crying/irritability	11	85
Absent of head movement control	13	100
Head lag	13	100
Recurrent respiratory infections	11	85
Abnormal BERA test compatible with disease in the brainstem level	13	100
Skull deformity or flattening	1	0.9
Nystagmus/Strabismus	13	100
skin abnormality*	0	0
cardiac or skeletal abnormality	0	0
markedly increased urinary secretion of ethyl-malonic acid	5	38
Deceased between 1-4 years‡	5	38

Table 1: The frequency of the various symptoms and signs in 13 cases of leuko-dystrophy. # Muscles of the central part of the body, not the limbs. * Neurofibromas, eruptions etc. ‡ life range of severe types of LD could be larger than 4 years. § Diagnostic sign for Tay-Sachs and Neiman-Pick diseases.

Type of LD	% of Truncal hypotonia	% of Eye abnormality	% of Abnormal BERA test	% of other characteristics
Peliazeus-Merzbacher disease*	high†	high	high	vary††
Mitchap 60 disease‡	high	high	high	vary
Metachromatic-leukodystrophy	high	high	high	vary
Refsum disease	high	high	high	vary
Zellweger disease	high	high	high	vary
Alexander disease	high	high	high	vary
Canavan disease	high	high	high	vary
Krabbe' disease	high	high	high	vary
Vanishing white matter	high	high	high	vary
Aircadi-Goutie'res syndrome‡	high	high	high	vary

Table 2: The prevalence of the triad of characteristics in the known types of leuko-dystrophy (LD). X-linked LD. † A major presenting symptom. †† less or slightly high frequent presenting symptom or sign such as irritability, epilepsy etc. ‡ Recently detected autosomal recessive LD, from 2009.

For this purpose, the medical files of a group of three infants, out of thirteen infants, who suffered from the same familial LD, were reviewed.

Case 1

N. Mais, three months old female, born weighing 3200 g, length 50 cm and head circumference 34 cm, after a full-term uncomplicated pregnancy, was referred to our attention by the "Mother and child care unit" because of inability to control her head movements. She was the first child born for two healthy 1st grade consanguineous parents, both Bedouins. Her mother, twenty years old, had a sufficient Rubella antibodies level before she became pregnant. Fetal movements were felt after the twentieth week of gestation.

N. Mais was born in February 2011; her APGAR score was 9/10. Her neonatal period was unremarkable. On physical examination, she was still appropriate for her age. No dysmorphic body features were noted. Her reflexes were at normal limits for age. The physical examination in the fourth month of her life revealed a loss of ability to turn head from side to side when she was in a prone position. Her head dropped at sitting position. Inability to make eye contact, with chaotic eye movements (nystagmus) appeared simultaneously with the head droppings.

When she was six months old, she was diagnosed by the neurologist as suffering from a congenital myopathy of metabolic or genetic origin and was sent to complete her metabolic and genetic investigations, without specifying a presumptive diagnosis.

At eight months old she was not able to turn from back to side. No eye contact. Hyper-reflexia was prominent. An ophthalmologist revealed "unlimited range of eye movements", with normal eye compartments. There was no cherry red spot in her retinas, [2]. Blood serum chemistry including liver enzymes and creatine phosphokinase (CPK) level, metabolic and endocrine evaluation were normal except a markedly increased urinary secretion of ethyl malonic acid [1,16]. Brain sonography at this age ruled out hemorrhages, or brain anomaly. MR Imaging, at age of thirteen months, revealed diffuse white matter disease of central hypo-myelination. Sequential BERA tests showed a lack of conduction of the electrical signal at the level of the brain stem [23,24]. Mutation analysis revealed a homozygous mutation, D29G, which encoded the mitochondrial Hsp60 chaperonin. This disorder was named Mitochondrial Hsp60 Chaperonopathy LD, or Mit Chap-sixty disease [1]. Follow-up MRIs were refused by parents.

Later, N. Mais suffered from recurrent apnea and swallowing difficulties which necessitated special assistance. When she was two years old, she entered gradually to a continuous coma state and died at home in April 2013, as the result of prolonged apnea at the age of two years and four months old. Many requests from parents to undergo genetic counseling before and during future pregnancies, including family planning, were rejected.

Case 2

N. M' a four months-old female, was born weighing 2600 g, after a full term uncomplicated pregnancy. Her APGAR score was 9/10 and she had mild physiologic jaundice with maximal total bilirubin level 12.2 mg%. Screening test for Auditory Brainstem Responses (ABR) at birth was abnormal in the right side. At this early age, her mother disclosed: "something is going wrong with my baby: her meals necessitated longer times and she had probably a difficulty to move the head".

N. M' was the fifth child of consanguineous Bedouin parents, fully immunized, carriers of the mutation for sickle cell anemia. Her second brother, four years old, suffered from a nephrotic syndrome. The other two brothers and one sister suffered from mild asthma. Her brothers and sisters had a normal head growth.

On physical examination, she was still adequate weight for her age. Her head circumference was under developed, 41 cm, without any dysmorphic body features, but uncontrolled head movements, staring eyes, persistent Moro reflex and hyper-reflexia were observed. No visceral organs enlargement was detected. When she was five months old, BERA test was compatible with abnormal brainstem function, and nystagmus was obvious; It was clear then that we are facing the same disease as in case 1. MR Imaging of brain showed diffuse hypo-myelination of the white matter. The examination of the mutation within a linked genomic interval on the long arm (q) of the second chromosome; (2q32.3-q33), revealed again the homo-zygotic mutation of the Mitochondrial Hsp60 Chaperon-pathy LD, as in case 1. From here to her death at 1.10 years old, a chain of other signs had

progressed simultaneously or consecutively "under our sight": The loss of the social interest, absence of smile, failure to thrive, later, at the short run, a further decay of muscular tone, spastic paraplegia, impossible swallowing and respiratory failure thereafter. Her mother had undergone tubal ligation as a step of safety. She asked to have genetic counseling anyway.

Case 3

At the first weeks of pregnancy, frequent requests from the young couple to undergo genetic counseling and specific genetic tests in order to rule out that the fetus is homozygous for the same Mitchap-sixty disease, as his sister N. Mais in the above case 1, were refused. The fetal screening sonography at 20 weeks of gestation was normal. Eventually, N.O was spontaneously born, full-term of normal pregnancy. His father was 24 years old and his mother was 22 y old. His birth weight was 2200 g. His APGAR score was 9/10. On physical examination he was small for his age, without dysmorphism. Not far from our expectations, the worst happened again. After he was considered "normal" well baby during the neonatal period, the same signs appeared in a successive manner after three months of age; the trunk hypotonia with head-lag, the uncontrolled eye movements were obvious. His first BERA test, which was partially abnormal, had changed to be completely abnormal at six months of age. The child was referred to the neurologic consultant who described him as an irritable baby, with occipital flattening and 45 cm head circumference (25 percentile) with "sub-normal" eye movements, mild hypotonia and borderline hypere-reflexia. His Babinski sign was normal for age. Brain MR imaging was refused by the parents. Biochemical tests and genetic screening were initiated early after the patient had displayed the above symptoms together with abnormal BERA test, revealing the same Mitochondrial Hsp60 Chaperone-pathy LD. He was at four months old at the time of mutation detection. Sleep disorder, irritability, ticklish crying, loss of social smile and interest had followed. Both parents had reckoned to their fault and agreed to implement one of the options available for the birth of a son or a daughter free of the mutation.

Parallel to reviewing the files of the three patients, we also reviewed the available literature in order to screen the most frequent clinical features of the majority of the LDs.

Results

So far, three infants had had the same disease characteristics. Table 1 shows the three most frequent characteristics of LD in our group of the three infants and in ten other patients with the same mutation from other Bedouin clan [1,17,18], and their minor characteristics of lesser frequency:

The three cases presented above can shed light on three major markers; the hypotonia of the trunk muscles, nystagmus and abnormal BERA test.

Actually, the above most frequent characteristics were similar to the signs that had been observed in the group of infants from a different Bedouin clan, which were described by Magen et al. [1]. This closeness of features between the two groups had really sparked the idea that the three infants in our group suffer from the same defect as that of the other Bedouin clan patients as in Magen's. Determining the mutation was really the right thing to do then.

Indeed, it took us nine months from the beginning of symptoms to final diagnosis of N. Mais whereas it took less than two months to diagnose the other two cases; N.M' and N.O., successively.

Table 2 shows the prevalence of the three prominent markers, namely, the hypotonia with phenomenal head droppings, nystagmus/strabismus, and abnormal BERA test, in each of the various known types of LD, according to the cited medical literature [11,14,15].

Discussion and Conclusions

The characteristics or markers of the diseases that cause abnormal production of the myelin layer of white matter, or its degradation, are numerous, but there is neither a single common denominator symptom for us to consider it as a pathognomonic sign for all these diseases, nor a unified approach to guide pediatricians and fasten diagnosis of these diseases. Review of the medical literature dealing with the already detected and named myelin disorders (Table 2) revealed that there are major non-specific characteristics, and other minor markers. We mean by "minor markers" as those symptoms and signs which are infrequent and not pointing to the brain.

Based on the above results in (Tables 1 and 2), we suggest that a combination of the following three major features: first, head lag or head droppings of the diseased infants, number two, early uncontrolled eye movements; i.e. nystagmus/strabismus, and number three, an abnormal conduction in BERA test which is compatible with a defective white matter in the brainstem level – in the presence or absence of the minor characteristics: irritability, inability to react socially, limbs spasticity, with normal levels of CPK and liver enzymes – is a triad of markers that will help clinicians to point on diagnosis of the group of the PMD and of the LDs in general.

We established the triad as "Mais-N-Nasser Triad" or "MNN Triad," when the name "Mais" should be pronounced as (Ma-is), will be in memory of the first baby that was diagnosed in our group, and the name "N- Nasser" is the name of the author of this article.

The novelty of this Triad stems from two facts: first, it was not described in the medical literature as a unique clinical tool in the algorithm for diagnosis of white matter diseases, second, being a relatively quick tool for sorting and diagnosis of the group of LD relying on symptoms and signs from which a patient suffers, when the next step will be deliberate to reach the exact name of the disease, by brain MRI and mutation search [9,25,26].

The "Mais-N-Nasser Triad" will serve pediatricians as an effective tool to diagnose diseases which cause trunk hypotonia. It seems possible to declare that everyone component of the Triad must be sought obsessively, over months to years, in a sick child for whom one or more of the following complaints are brought to our attention:

a. Truncal hypotonia expressed as head droppings and non-physiologic head-lag.

b. Nystagmus,

c. Deafness expressed by abnormal BERA test.

Only when the triad seems to be incomplete during few years of follow-up and further investigations such as MR imaging, did not show brain hypomyelination, then efforts should be directed to search other diagnosis than LD.

The case of N.H., a seven months old male infant who was born to consanguineous parents who belong to the same Bedouin clan as the above mentioned three cases, and was suspected to have the same LD mutation, for he had severe conductance delay in BERA test and mild truncal hypotonia, but did not suffer from eye problems, stresses that the absence of one component of the so called MNN Triad; the absence

of nystagmus in his case, makes the diagnosis of LD mostly impossible, as was proved by a negative mutation analysis at eight months old, and by brain MRI at twenty two months old, disclosing the Mondini malformation of the inner ears, but normal brain structures.

When the triad is complete, with all of its three components, the patient is most probably suffering from brain myelinization defect. Verifying the diagnosis by MR Imaging and genetic search for mutations could be done immediately then.

For example, an infant, whose BERA test had detected a delayed or absent conductance at the level of brainstem, as an indication of deafness, should he be followed up and checked periodically, searching for the existence of the remaining two components of the MNN Triad; truncal hypotonia and nystagmus; as the marker of LD, a fortiori when there is a family history of these diseases.

Summary

We consider the "Mais-Nadim-Nasser", or its short name "MNN Triad", as the main diagnosis leading phenomenon of the LDs.

In families with history of LD diseases, every descendent who suffers from convulsions, hyper-reflexia, spastic paraplegia, excessive crying and irritability, bizarre eye movements, deafness and loss of social reactivity, should be traced periodically to get on the major clinical features of the triad: trunk muscular hypotonia, nystagmus and abnormal BERA test, since this triad is an applicable tool for early diagnosis of these familial diseases.

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