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Review Article

White Matter Disorders in Childhood. A Perspective

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Abstract

This review study restores the recently published article about the clinical diagnosis of central white matter disorders in infancy and childhood.

Generally, clinical descriptions of white matter disorders suffer from a flood of clinical features, that seem unrelated one-to-another; the result of widespread distribution of white matter through the CNS. Thus, generally, clinicians find it difficult to select a pointing single pathognomonic clinical landmark of a central myelin disorder.

Theoretically, the primary defect of hypo-myelination is not selective for only one anatomical level of white matter. Thus, it can hit three definite brain organs, mainly, sub-cortex, optic tracts (and olfactory tracts) and brainstem, simultaneously or sequentially.

The defect of myelination at those three levels is clinically expressive among other sites of central white matter, and manifest as three major clinical features. Those features are the most prevalent in all leukodystrophies. Other features are sequelae and minor expressions.

We believe that, the pathway to diagnose white-matter disorders is straightforward, in presence of the triad of major signs. The start point is finding of hyperreflexia of patella tendon, along with spastic paraplegia, because they rule out lower motor neuron disease. Beyond these findings, the diagnosis of a central white matter disease is at simple.

The disclosure of one major feature in a certain infant should be an impetus to clinicians to follow-up infants and expect the other two during childhood and adolescence. The complete triad is a highly specific for all leukodystrophies, long before utilizing ancillary testing

Keywords: *White matter disorders. Myelin disorders. Leukodystrophies. Hypereflexia and spastic paraplegia. Hypotonia. Nystagmus. BERA.*

Abbreviations

SNHL: Sensorineural Hearing Loss; LD: Leukodystrophy; BERA: Brainstem Evoked Response Audiometry; PMLD: Pelizaeus-Merzbacher-Like Disease; OAE: Oto-Acoustic Emissions

Introduction

The spread of white matter in the central and peripheral nervous systems is extensive. It is non-surprising, then that the clinical expressions of white matter disorders - also known as leukodystrophies or myelin disorders - deluge the medical literature. However, there is no common denominator, or a sole pathognomonic sign pointing to those disorders, among those clinical markers [1-5].

Such mixture of scattered symptoms overlaps to symptoms of other neural diseases, often masks the diagnosis of white matter disorders, and makes the diagnosis of those diseases, at bedside, a tough challenge [6-9].

The latest „Global Leukodystrophy Initiative consortium" had defined the white matter disorders, as ‚a heritable disorder affecting the white matter of the central nervous system with or without spinal nervous system involvement'.

In the other hand, the classification of them by ‚primary and acquired diseases of the white matter' is an equally accepted definition [3,5,7,8].

The primary central white matter disorders are mainly a result of genetic defects of the glia cells, mainly, the oligodendrocytes' specific-genes. Those defective genes inhibit the myelin production. Other types of the glia cells, namely, astrocytes, ependymal cells, and microglia, which wrap the axons, might be harmed too [5].

Nevertheless, those primary genetic defects do not harm the neurons themselves. Hence, inherited storage disorders that, specifically affect the neurons, such as GM1 and GM2 gangliosides, cannot be included, in no way, under any definition or title, regarding the primary white matter diseases [1,2,8,9].

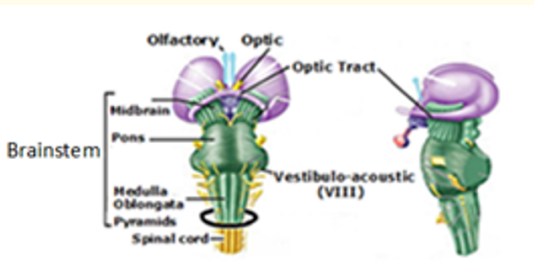
To make things clearer, by definition, all leukodystrophies [LDs] are the product of genetic defects in the glial cells. Some of those gene defects lead to enzymatic deficiencies, which eventually prevent myelin production, within the glia cells; as, for example, the Arylsulfatase deficiency in the Metachromatic leukodystrophy [10].

The acquired central white matter disorders are beyond the scope of this review, although it is worth mentioning that they are essentially immune-mediated. Examples are, Multiple Sclerosis, acute disseminated encephalomyelitis, Schilder disease and secondary CNS vasculitis [2,11], where both, the grey matter neurons, as well as white matter glia cells are immunologically injured.

At this paper, we offer our review of a recently published perspective about white matter disorders. Our candidates are principally, children with hypotonia, irreversible nystagmus and sensorineural deafness.

Anatomically, central white matter exists in three main and well-defined brain organs (or levels):

A. The sub-cortical level and nuclei efferents.
B. The superior cranial nerve tracts, namely, the optic tracts and the olfactory tracts, which pass through the brain [12-14]).
C. The brainstem with its three parts, Midbrain, Pons and Medulla-Oblongata, including all the other ten cranial nerves passing through it (III-XII nerves), which are represented by the vestibulo-cochlear nerve (Figure 1).



Optic Tracts Anatomical Relationship. Note that almost all the cranial nerves pass through The brainstem, except for the Olfactory (1st nerve), And the optic (2nd nerve), which pass through the brain itself. [Image was edited from Google images] [2016]

Figure 1

Functionally, poor conduction of the neuronal signals is the major outcome of all the white matter disorders [5,6,15].

The following case report could help us understand the subject, in an easier way, where it highlights the real chronology of development of the clinical signs that makes white matter disorders' diagnosis at hand.

Case report of K

K. had no perinatal problems before she attended our peripheral community-clinic, at the age of 5 months, because of continuous crying and 'inability to control the movements of her head, while nursing'. Her weight and length were adequate for gestational age. Inspection at this age revealed that, her head moved to every side as if it swung upon a stalk. Rapid pendula movements of eyes that manifested three months later were ominous.

We referred K. to the Neuro-Ophthalmologist, who responded as follows: „No dysmorphism. Her eyes did not follow an object and no social smile. Her head circumference had severely retarded. The floppiness of axial muscles of neck and back were obvious. Deep tendon reflexes were very alert and spastic paraplegia of limbs was obvious. No cherry red spot in retinas".

Continuous crying was a main complaint. She was blind. We observed the inability to suck and to swallow, at every visit. K. failed to thrive and her head circumference at one-year-old was still 41 cm (Figure 2). She was fed per a gastric tube for some time, and then by percutaneous-endoscopic-gastrostomy. Chronic bronchitis dominated her last visits.

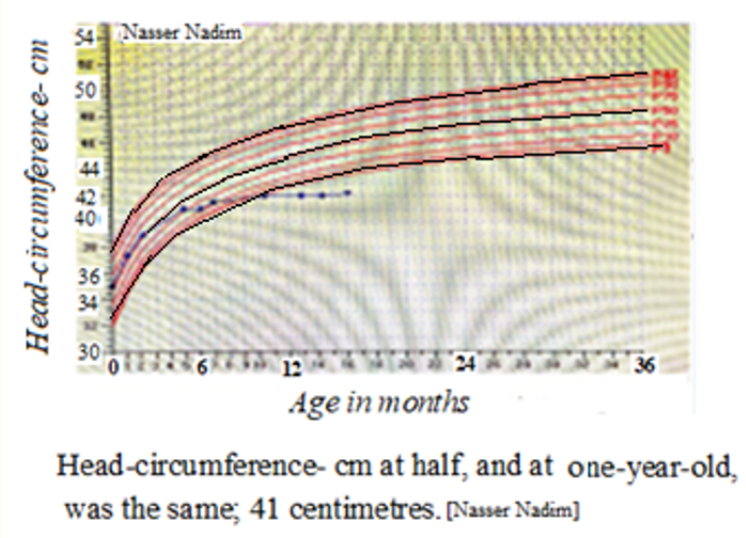
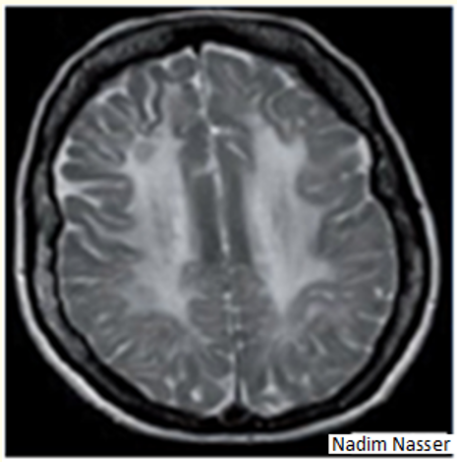


Figure 2

A Brainstem evoked response audiometry [BERA] test at six months of age was 'partially normal'. However, the repeated BERA at nine months-old had shown a complete impediment of voice conduction at the level of the brainstem. However, tympanometry test and the Oto-Acoustic emissions (OAE) were normal.

MRI of brain at thirteen months of age, showed specific perturbation of myelin-genesis, without metachromatic stain; a characteristic image of most LDs (Figure 3).



Brain MRI showing characteristic changes of the white matter demyelination. [2012]

Figure 3

A homozygous missense mutation D29G, of *HSPD1* gene was identified [9,16,17]. It is a Pelizaeus-Merzbacher-Like Disease, shortened as "PMLD".

This case report proves that, it is necessary to continue follow-up, in outpatient clinics, of every newborn belonging to K's tribe, and expect for the appearance of the aforementioned major characteristic expressions.

The clinical perspective

Our target is identifying white matter disorders in suspected kids, relying on clinical landmarks, those that we disclose at patient's bedside. It is a preliminary stage before exploiting advanced ancillary testing, such as brain MRI, and chromosomal analysis, multiplex ligation probe amplification, whole exome sequencing, and whole genome sequencing [1,17-19].

Acquaintance with the white matter disorders' landmarks is the first step.

We expect that, clinical features of the hypo-myelination defect within every level of the brain white matter are different.

Injuries at sub-cortical white matter will cause a distinct motor delay, due to hypotonic axial muscles of back and neck. The patient will manifest by a prominent head-lag and titubation (swinging movement of head, as like a ball on a stalk).

A myelin defect of the optic tracts manifests by horizontal nystagmus, (as opposed to downbeat nystagmus caused by cerebellar disease).

A myelin defect of the olfactory tracts is not apparent in infants, although it exists.

A de-myelination disorder at the brainstem level leads to cranial nerves dysfunction, however, their symptoms are not detectable in infants, except for the vestibulo-acoustic, VIII nerve injury, which causes, eventually, a complete absence of conduction of the auditory information, to the temporal hearing center, namely, sensorineural hearing loss (SNHL). We shall consider SNHL as the representative of all the loss of sensory and motor functions of the III-XII cranial nerves injuries, because, among senses, it is the most feasible to document by means of BERA encephalography, called also, the ‚Brainstem Evoked Response Audiometry' [12,14].

It turned out that, axial muscles' hypotonia, pendula nystagmus and sensori-neural hearing loss are the most common combination of clinical expressions in all known LDs.

However, every one LD might differ from another type of LD, by one or more of characteristic features [5].

Hypo-myelination disorder has sequelae, which could manifest as non-neurologic and/or as neurologic features.

Examples of non-neurological sequelae include are, majorly, failure-to-thrive, which is an end-result of every one of the three major malfunctions; namely, head-lag with head titubation, nystagmus and deafness.

Underdevelopment of head circumference is another non-neurologic feature due to loss of brain tissue following the insufficient production and de-myelination of central myelin.

Neurologic sequelae include spastic paraplegia and hyperreflexia, which are the late neurologic complication caused by injury to axons of upper motor neurons [20,21]. Blindness is the product of injured optic tracts, whereas, deafness, absent swallowing reflexes and recurrent aspirations of food, are the product of hypo-myelination injuries to the cranial nerves, which pass through the brainstem, including the bulbar XI, X, XI, XII nerves [2,3,5,6].

Irritability and excessive crying could be secondary to hunger, thirst, or from the primary gliopathy in such disorders [5,22].

Convulsions in primary LDs are rare, but are not impossible; however, they are more common in grey matter diseases and in the acquired LDs [11].

With the presence of only one clinical expression, at patient's bedside, a clinician cannot conclude that a certain infant suffers from a white matter disorder. He needs the escort of other features, for determining the diagnosis.

Discussion, Conclusion and Recommendations for Practice

When a group of infants share similar clinical markers of white matter disorder, and have a similar family history of a certain type of leukodystrophy, it makes us closer to the diagnosis of this disorder, long before utilizing ancillary testing of the genetic chips, exomes and whole genome.

As it is clear, axial hypotonia is not the only feature in central white matter diseases, and may not be the first appearing feature. There are other major features, of which pendulum eye movements and sensori-neural hearing loss, have a prominent diagnostic value. Although other 'minor' features and sequelae are significant markers pointing towards clinical diagnosis.

Clinicians should wait for

a) The appearance of axial hypotonia, represented by head-lag and titubation,
b) Wait to pendula nystagmus,
c) Repeat BERA examination intentionally, every three months, when the initial BERA had 'passed', or even 'partially normal', in a certain patient. It is inevitable that BERA will 'fail' in infant life, or manifest later to in childhood, when, in retrospect, it turns out that the baby has LD.

Based upon three clinical features, the result of defects in three brain organs, this perspective has been published in 2017, in the Journal of Genetic Syndromes and Gene Therapy, under the title: "Mais-Nadim Nasser Triad". It is a triad of the aforementioned clinical findings, and is useful for bedside diagnosis of all LDs, early before carrying out ancillary testing.

Each type of leukodystrophy may have its certain additional characteristic/s, additive to the triad features. Examples are the following.

In Alexander LD, for example, the accumulation of eosinophilic hyaline bodies in the mini structures of the vascular bed of central white matter causes enlargement of head, in the first year of life, in parallel to the triad of LD features. However, the head circumference declines thereafter, due to de-myelination .

In the metachromatic LD, a metachromatic stain of the brain's white matter, which appears as bright whit matter in MR images, characterizes this LD, side-by-side with the triad of axial hypotonia, nystagmus and SNHL.

In the Adreno-LD is another example, at which the appearance of primary adrenal insufficiency (Addison's disease), and possible deterioration towards an Addisonian crisis, with severe hyponatremia dehydration, among other metabolic dysfunctions [24].

In spite the fact that, a myelination defect could hit at every nerve fiber where myelin exists, however, most of the affected cranial nerves, do not clinically manifest. Consequently, we cannot monitor them in patients under three years of age. For example, in infants, we have no ancillary means to evaluate the ability of an injured olfactory nerve to identify odor and discriminate it.

Moreover, there are only few auxiliary laboratory and imaging tests, which can confirm the presence of a myelin disease. The BERA Encephalogram is a tool, by which we can locate a neural injury at the level of brainstem. The brain MRI can disclose gross changes in the white matter disease, which are characteristic for LDs, including some characteristics of certain types of these disorders, no more [25]. The final verification of the diagnosis culminates by the detection of the mutation of white matter disorders.

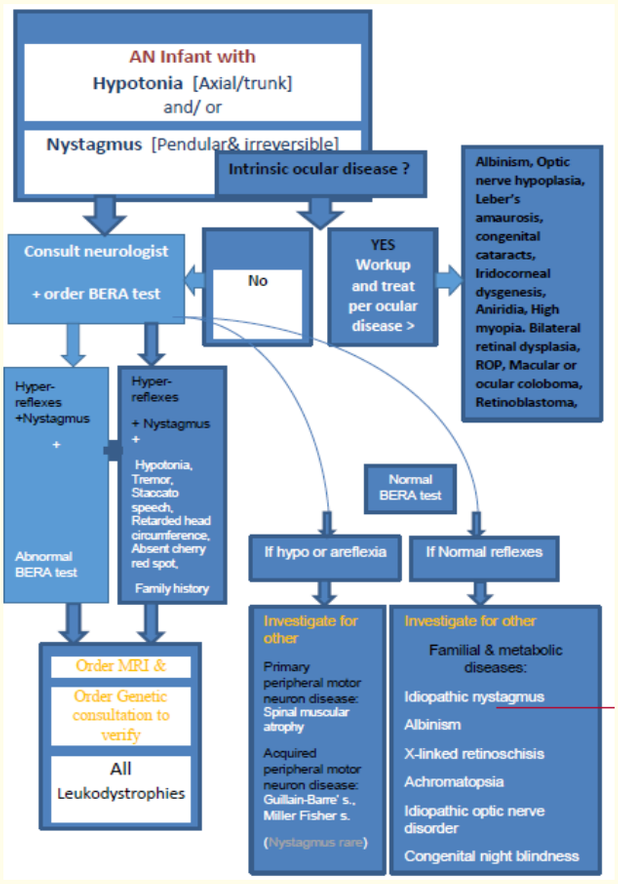
The rarity of white matter disorders naturally makes pediatricians and primary care physicians, refrain considering them, as the first possible etiology of delayed motor activity in small kids. Their investigation toward such etiology begins usually after exhausting all the other reasons [26,28].

However, clinicians, ophthalmologists and otolaryngologists, should take into account, from the outset, a white matter disorder among first-line etiologies, when infants suffer from one or more features of axial hypotonia, pendulum nystagmus or abnormal BERA test.

We dedicate our proposal of the new clinical perspective of the central white matter diseases, in childhood, to primary care physicians, neurologists and otolaryngologists, as an ancillary tool for clinical diagnosis of white matter disorders.

Practice

The following steps to carry out for the differential diagnosis of a hypotonic infant [see also flowchart]:



Flow chart

1- Find out family history of inherited diseases.

2- Identify if the patient suffers from hypotonia of back and neck muscles.

3- Elicit hyperreflexia and spastic paraplegia. They are the classic sign of a CNS injury, the so-called the «upper motor neuron», as opposed to peripheral nervous injury [27].

a) [Positive findings mean that, central nervous system disorder of the upper neuron and/or its axons; (grey matter, or the white matter), is now obvious].

4- Differentiate between possible injuries of grey matter, versus white matter, with the help of the Neuro-Ophthalmologist. Each has its characteristic findings. [The clinical findings, in favor of a primary white matter disorder, versus grey matter, are shown in table 1].

1-	Gradual appearance (months to years) of other symptoms and signs, like hypotonia, hearing impairment or eye-movement aberrations, staccato speech and intentional tremor.
2-	The retinas are normal.
3-	The underdevelopment of head circumference, as shown by percentile charts.
4-	Convulsions are rare and late.

Table 1: *The characteristic features of a white matter disorder, which help to differentiate it from a gray matter disorders.*

If convinced that a white matter disorder is the case, then:

1. Locate the level, at which the injury occurred in the central nervous system. The finding of very high thresholds of over than 60 decibels in BERA, via bone conduction, is consistent with an injury at the brainstem level. [The Cortical Evoked Response Audiometry [CERA] can locate an injury at the level of the auditory center, which is situated in the temporal lobe].
2. In a certain child, the combination of axial hypotonia, neural hearing loss, along with the appearance of pendular nystagmus, makes the diagnosis reachable for any type of LD, even though, other leukodystrophy's type-specific characteristics may exist.
3. Now order a conventional MRI, or its complementary, the so-called Proton Magnetic Resonance Spectroscopy (MRS), since they proved to be valuable tools to establish the diagnosis of leukodystrophies [25,29].
4. When MRI of the brain shows the characteristic image of a LD, it is time to carry out genetic verification of diagnosis of a genetic myelin injury. Although, in our opinion, when we have a family history of LD, along with the aforementioned triad of features, we can give up carrying out brain MRI, and early investigate the mutation by means of the specific genetic tests [1,19].

Bibliography

1. Van der Knaap MS. "Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach". *Radiology* 213.1 (1999): 121-133.

2. Appleton and Lange Book. "Current Pediatric Diagnosis and Treatment". 13th Edition, Hay, Groothuis, Hayward, Levin, Pages 676, 883.

3. Nelson Textbook of Pediatrics. Liegman, Berhman, Jenson, Stanton, 18th Edition. Saunders, an imprint of Elsevier Inc. (2007): 2499-2504.

4. Heim P. "Leukodystrophy incidence in Germany". *American Journal of Medical Genetics* 71.4 (1997): 475-478.

5. Gordon HB. "The leukodystrophies". *Seminars in Neurology* 34.3 (2014): 312-320.

6. Kohlschütter A. "Childhood leukodystrophies: a clinical perspective". *Expert Review of Neurotherapeutics* 11.10 (2011): 1485-1496.

7. Numata Y. "Epidemiological, clinical, and genetic landscapes of hypomyelinating leukodystrophies". *Journal of Neurology* 261.4 (2014): 752-758.

8. Vanderver A. "Case definition and classification of leukodystrophies and leukoencephalopathies". *Molecular Genetics and Metabolism* 114.4 (2015): 494-500.

9. Haoran Ji. "Hypomyelinating disorders in China: The clinical and genetic heterogeneity in 119 patients". *PLOS One* 13.2 (2018): 0188869.

10. Mackenzie A Robinson. "Roles of microglia in brain development, tissue maintenance and repair". *Brain* 138.5 (2015): 1138-1159.

11. Brendan JK and Moses R. "Seizures in Patients with Multiple Sclerosis Epidemiology, Pathophysiology and Management". *CNS Drugs* 23.10 (2009): 805-815.

12. Richard LD. "Tests of human olfactory function: Principal components analysis suggests that most measure a common source of variance". *Perception and Psychophysics* 56.6 (1994): 701-707.

13. Zald DH. "Functional Neuroimaging of the Olfactory System in Humans". *International Journal of Psychophysiology* 36.2 (2000): 165-181.

14. Kivity S. "Olfaction - A Window to the Mind". *Israel Medical Association Journal* 11.4 (2009): 238-243.

15. Nasser Nadim H. "'Mais-Nadim Nasser Triad', a Useful Marker for Leukodystrophies Diagnosis". *Journal of Genetic Syndromes and Gene Therapy* 5 (2014): 242.

16. Magen D. "Mitochondrial hsp60 chaperonopathy causes an autosomal-recessive neurodegenerative disorder linked to brain hypomyelination and leukodystrophy". *American Journal of Human Genetics* 83.1 (2008): 30-42.

17. Saty SM. "Chromosomal Microarray Analysis for Intellectual Disabilities. Template Coverage Policy". *American Academy of Neurology* (2013).

18. Van der Knaap MS and Valk J. "Magnetic resonance of myelination and myelin disorders". New York: Springer (2005).

19. Vanderver A. "Whole exome sequencing in patients with white matter abnormalities". *Annals of Neurology* 79.6 (2016): 1031-1037.

20. Fink JK. "The hereditary spastic paraplegias. Nine genes and counting". *Archives of Neurology* 60.8 (2003): 1045-1049.

21. Reid E. "Science in motion: Common molecular pathological themes emerge in the hereditary spastic paraplegias". *Journal of Medical Genetics* 40.2 (2003): 81-86.

22. Loggia ML. "Evidence for brain glial activation in chronic pain patients". *Brain* 138.3 (2015): 604-615.

23. Prust M. "GFAP mutation, age at onset, and clinical subtypes in Alexander disease". *Neurology* 77.13 (2011): 1287-1294.

24. Nasser NH and Nasir NN. "Cortisol Push to a Stuporotic Severe Hyponatremic Child Nonresponsive to NACl Rehydration". *Academic Journal of Pediatrics and Neonatology* 4.5 (2017): 555703.

25. Haaga JR. "CT and MRI of the whole body". Mosby (2009).

26. Henneke M. "Clinical neurophysiology in GJA12-related hypomyelination vs Pelizaeus-Merzbacher disease". *Neurology* 74.22 (2010): 1785-1789.

27. Willison HJ., *et al*. "Guillain Barre Syndrome". *Lancet* 388 (2016): 717-727.

28. Bonkowsky JL. "The burden of inherited leukodystrophies in children". *Neurology* 75.8 (2010): 718-725.

29. Michelson DJ. "Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society". *Neurology* 77.17 (2011): 1629-1635.

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