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# Clinical and Genetic Study of Children with White Matter Diseases

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**Abstract:** Background: White matter disorders or leukoencephalopathies comprise all disorders that exclusively or predominantly cause affection of the white matter of the brain. Many leukodystrophies are degenerative in nature, their clinical course is mostly progressive. Aim of the study: Study patients of white matter diseases in order to create a new algorism for white matter diseases based on clinical and radiological presentation. Patients and methods: In this study, we describe the clinical and neuro-radiological findings of 115 patients with white matter diseases. Age spectrum is from six months to 12 years old, putting in consideration the correlation of white matter development with age during the first 2 years of life. Brain MRI demonstrated deep white matter affection in all patients that varied in severity and distribution. Results: Canavan disease encountered the most common neurodegenerative disorder in our study (22.6%). Conclusion: we present a large cohort of patients with the characteristic clinical and brain imaging findings of white matter diseases. Moreover, we create current useful, algorithms for white matter diseases hoping to be helpful for the treating neuropediatricians and neurologists to make a definitive diagnosis and to decrease burden to patients and families with uneventable investigations who usually are deteriorating from a severe and progressive neurological syndrome.
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**Keyword:** Leukodystrophies, adrenoleukodystrophy

## 1. Introduction:

The term ‘‘leukodystrophy” is defined as the degeneration of the brain’s white matter. Leuko means white and dystrophy means defective growth and nutrition. [(1)]The last decade has witnessed a huge increase in the number of defined leukodystrophies (LDs), also owing to a diagnostic approach combining magnetic resonance imaging pattern recognition and next generation sequencing. They are group of disorders that are characterized by: (a) genetic basis; (b) progressive condition, (c) predominantly confluent involvement of the central nervous system (CNS) white matter and (d) primary disease of myelin and myelin generating cells. [(2)]The inheritance pattern depends on the type of white matter disorder and its related etiology. Most heritable white matter disorders are inherited as an autosomal recessive pattern, autosomal dominant, x-linked and mitochondrial patterns have also been reported [(4)]. The age of presentation of different types of white mater diseases ranges widely from the neonatal period to adulthood. Generally, it presents early in life, but age at onset of symptoms has a wide range from childhood through adolescence [(6)]. Clinically, there is a wide range of signs and symptoms, the most common is deterioration or regression of neurologic and cognitive function, motor delay, hypotonia or spasticity, and seizure in the initial stages of the disease. However, some have stationary course without deterioration but with minimal improvement [(7)].

**Aim of the study:**

1-Study patients of white matter diseases in order to create a new algorism for white matter diseases based on clinical and radiological presentation.

2-Determine the etiology which is important to serve for proper genetic counseling and future prenatal diagnosis.

## 2. Patients and Methods:

The present study included 115 patients referred to the neurogenetics clinics at National Research Centre (NRC) for diagnosis and counseling. All patients were subjected to a full medical history, including prenatal, natal and postnatal histories with special emphasis on developmental history, and associated neurological deficits. Three generations pedigree construction, complete general examination,

full neurological assessment and basic anthropometric measurements (head circumference, height and weight) were done. Brain MRI was performed to all patients with thorough discretion of all details. Other investigations included: CPK, EEG, auditory brain stem evoked potential (BAEP), ophthalmological evaluation, visual evoked potential (VEP), electroretinogram (ERG), electromyograhy (EMG) and nerve conduction velocity (NC) and biochemical investigations were also performed to selected patients according to clinic-radiological diagnosis. Molecular analysis by target gene sequencing was done for patients with Canavan disease (ASPA gene), X-linked adrenoleukodystrophy (ABCD1 gene) megalencephaly leukoencephalopathy and cortical cyst (MLC1 gene and HEPACAM gene), and Pelizaeus Merzbacher disease (PLP1gene) based on identified clinical and radiological criteria of the elected disease.

**3. Results:**

**Table (1):** Diagnosis distribution among the studied groups:

| **Diagnosis** | **No.** | **%** |
|---|---|---|
| 1-Degenerative brain disease with white matter affection | | |
| Metachromatic leukodystrophy with low Aryl sulfatase | 11 | 9.6 |
| Metachromatic leukodystrophy with normal Aryl sulfatase | 2 | 1.7 |
| Krabbe disease | 3 | 2.6 |
| Canavan disease | 26 | 22.6 |
| Alexander disease | 1 | 0.9 |
| Pelizaeus Merzbacher disease | 1 | 0.9 |
| GJC2 | 4 | 3.5 |
| X-linked Adrenoleukodystrophy | 5 | 4.3 |
| 2-Degenerative brain disease with grey matter affection | | |
| Tay sachs disease | 4 | 3.5 |
| Ceriod lipofusinosis | 11 | 9.5 |
| 3-Brain malformations | | |
| Cobblestone lissencephaly | 2 | 1.7 |
| GPR56 | 4 | 3.5 |
| 4-Congenital muscle dystrophy | | |
| Congenital muscle dystrophy with lissencephaly | 2 | 1.7 |
| Muscle eye brain disease | 2 | 1.7 |
| Congenital muscle dystrophy without lissencephaly | 2 | 1.7 |
| 5-Hypomyelination with congenital cataract (HCC) | 8 | 7.0 |
| 6-Megalencephalic leukoencephalopathy with subcortical cyst (MLC) | 8 | 7.0 |
| 7-PYCR2 | 14 | 12.2 |
| 8-Non classified White Matter Disease | 5 | 4.3 |

Among 115 patients, Canavan disease was found to be the most common neurodegenerative disorder in our study and account for (22.6%). Subsequently, PYCR2 gene related hypomylenation leukodystrophy (12.2%). Metachromatic leukodystrophy (11.3%) followed by neuronal ceriod lipofusinosis (CLN) (9.5%), hypomyelination with congenital cataract (HCC) and megalencephalic leukoencephalopathy with subcortical cyst (MLC) (7.0%), adrenoleukodystrophy (4.3%), brain malformations and congenital muscular dystrophy (5.2%), Tay Sachs disease (3.5%), Pelizaeus Merzbacher disease like (4.3%) and Pelizaeus Merzbacher disease (0.9%). (Table 1)

**Clinical data:**

One hundred and fifteen patients with white matter diseases among the attendants of the Genetics Clinic and neurogenetics clinic at the National Research Centre (NRC) were evaluated. Seventy patients were males (60.9%) and 45 females (39.1%), their ages ranged from six months to 12 years. The median age of disease presentation in our study demonstrated that the majority of patients were in the infantile and the late infantile groups of childhood leukodystrophies as disease onset occurred in the first year of life (68.7%). From them (64.3 %) occur in the first 6 months of life and between 1 and 5 years of age (31.3%). Seventy two patients had a progressive course of the disease (62.6%) (neurodegenerative disorders) and 43 patients with a stationary course (37.4%). Positive parental consanguinity was recorded in 103 patients out of 115 (75.41%) and a history of similarly affected family members were noted in 40 families (34.8%). The majority of cases in our study

presented with a combination of cognitive delay or learning difficulties and motor problems (60.9%), while (39.1%) present with loss of previously acquired milestones associated with either normal or regressive of their mental abilities History of seizures recorded in 35 patients as a first presentation in our study (30.5%). Myoclonic fits were the most common presenting form (14.8%) followed by tonic seizures (7.8%), focal and generalized tonic clonic seizures (1.8%) of cases (Table 2).

**Table (2):** Clinical data of patients

| Clinical Data | N | % |
|---|---|---|
| Sex | | |
| Male | 70 | 60.9% |
| Female | 45 | 39.1% |
| Age | | |
| < 1 y | 12 | 10.4% |
| 1-5 y | 84 | 73.1% |
| 5 – 10 y | 16 | 13.9% |
| > 10 y | 3 | 2.6% |
| Onset | | |
| First year of life | 79 | 68.7% |
| 1st 6 m | 74 | 64.3% |
| 1-5 y | 36 | 31.3% |
| Consanguinity | | |
| +ve | 103 | 89.6% |
| -ve | 12 | 10.4% |
| FH | | |
| +ve | 40 | 34.8% |
| -ve | 75 | 65.2% |
| Molar milestones | | |
| delayed | 70 | 60.9% |
| regression | 45 | 39.1% |
| Mental milestones | | |
| Delayed | 66 | 57.4 |
| regression | 22 | 19.1 |
| normal | 27 | 23.5 |
| Anthropometric | | |
| Macrocephalic | 39 | 33.9 |
| Microcephalic | 14 | 12.2 |
| FTT | 14 | 12.2 |
| Tone & Reflexes | | |
| Hypertension with Brisk reflex | 54 | 47% |
| Hypertension with absent reflex | 60 | 52.1% |
| Preserved tone & reflex | 1 | 0.9% |
| Extra-pyramidal (Dystonia) | 14 | 12.2% |
| Seizures | | |
| GTC | 2 | 1.8 |
| Myochronic | 17 | 14.8 |
| Tonic | 9 | 7.8 |
| Focal | 6 | 5.2 |

On examination, basic growth parameter showed failure to thrive (underweight) (> -3 SD) in 14 cases of PYCR2 gene mutation (12.2%). As regard head circumference, Canavan disease and megalencephaly leukoencephalopathy with subcortical cyst (MLC) both present with macrocephaly (> +2SD) (39 patients). Both disorders differentiated according to onset of disease, course and severity of white matter in MRI. PYCR2 gene related disease (hypomyelination leukodystrophy type 10) and Aicardi-Goutières syndrome (AGS) (14 patients) (12.2%) presented with microcephaly (> -3SD). The rest of patients (N=48) were with normal head size (41.7%).

Neurological examination identified hypertonia (47.1%), hypotonia (52.1%) with brisk reflexes in (62.8%), with hyporeflexia in (26.1%) and with preserved reflexes in rest of patients. Extrapyramidal manifestations namely dystonia was more frequently in cases of PYCR2 and Krabbe disease (12.2%).

**Radiological data:**

Brain MRI showed demyelination of the white matter in periventricular region in all patients varied from mild periventricular which represent (10.4%), moderate periventricular represent only (3.5%) while severe periventricular represent the majority of cases (86.1%) mostly cases of Canavan disease.

Fig (1) different scans of patients with white matter disorders showing severity and distribution of white matter.

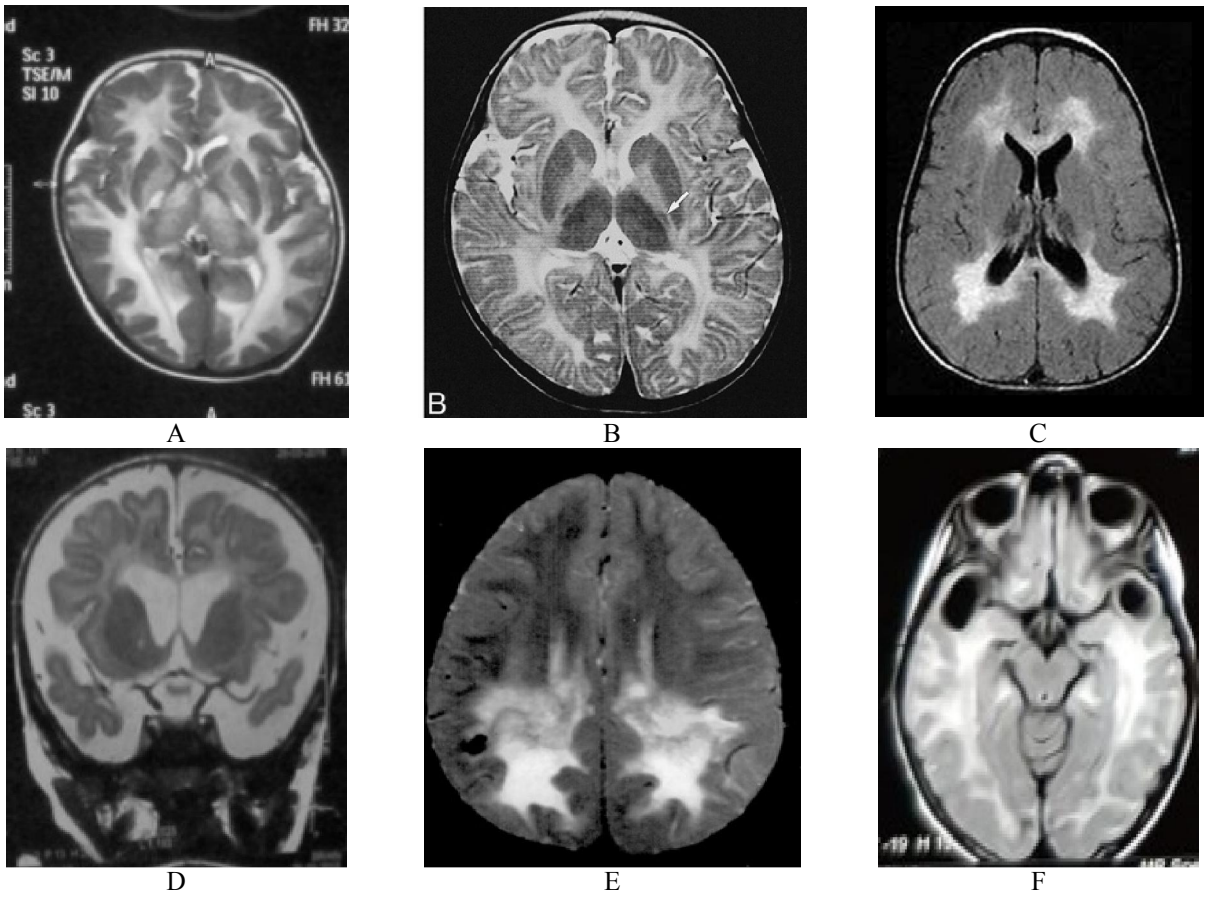
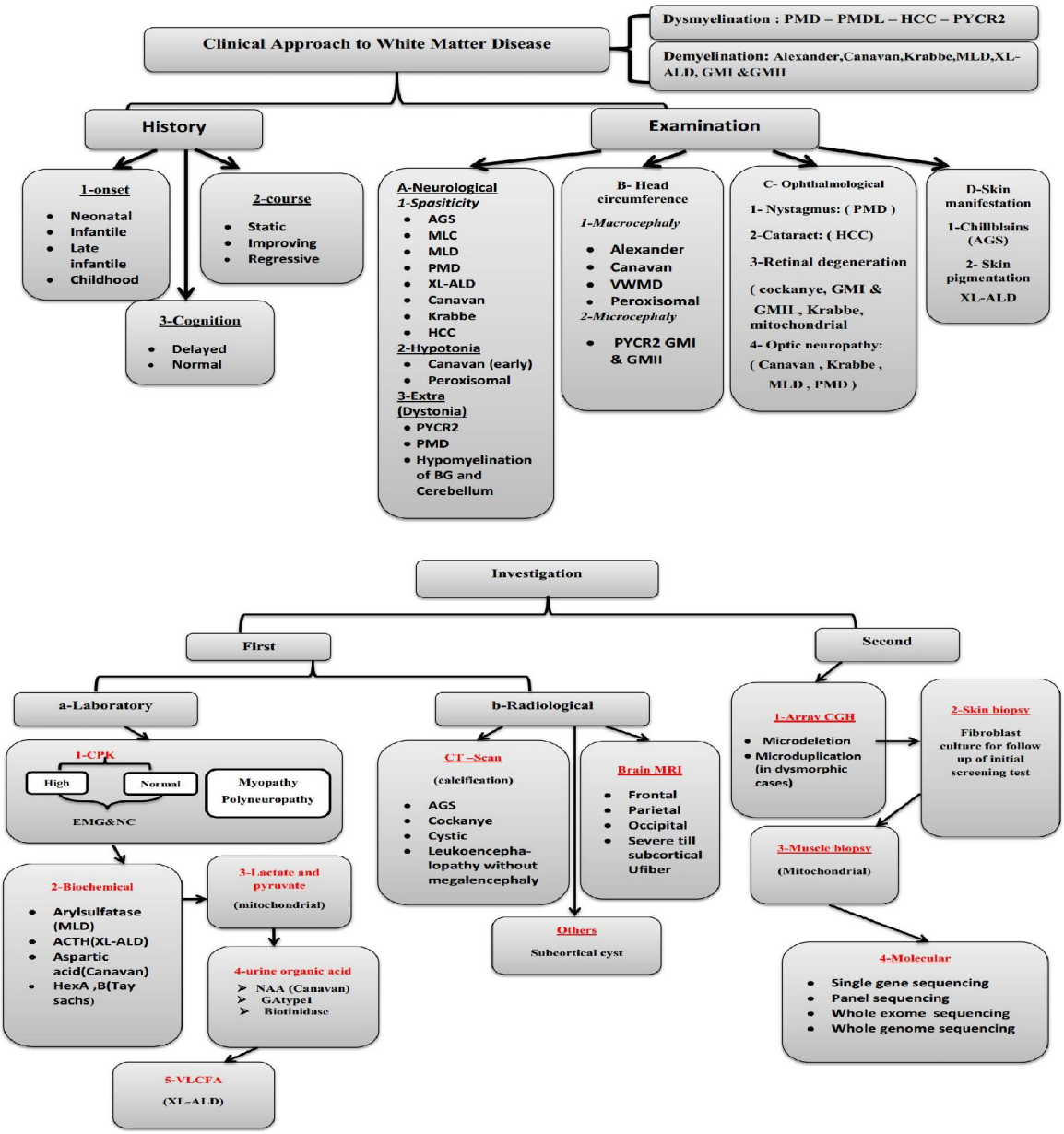



Figure 1; shows (A) canavan diseases, (B) Pelizaeus Merzbacher disease, (C) metachromatic leukodystrophy, (D) PYCR 2, (E) x-linked adrenoleukodystrophy, (F) megalencephalic leukoencephalopathy with subcortical cyst (MLC).

Finally we create an algohrism aiming to help the treating neuropediatricians and neurologists to make a definitive diagnosis, more definitive family counseling, prevents further worry about the diagnosis and to decrease burden to patients who usually are deteriorating from a severe and progressive neurological syndrome.




## 4. Discussion:

Leukodystrophies are a group of inherited disorders affecting white matter of the central nervous system with or without peripheral nervous system involvement. [8] These disorders are usually characterized by glial cell or myelin sheath abnormalities. [9] The genetic etiology of leukodystrophy and leukoencephalopathy is extremely heterogeneous, ranging from monogenic causes with little or no influence from environmental factors to genetically complex forms [11]. Childhood leukodystrophy are a growing category of neurological disorders in pediatric neurology practice. With the help of new advanced genetic studies such as whole exome sequencing (WES) and whole genome sequencing (WGS), the list of inherited childhood white matter disorders has been increased to more than one hundred disorders. [13]The incidence rate of leukodystrophy varied from 1.2/100 000 children in a study conducted by **(Vanderver et al., 2012)** in Washington, 2/100 000 children determined by **(Heim et al., 1997)** in Germany, 3.1/100 000 live births in a study by **(Stellitano et al., 2016)** in the United Kingdom, to 1/7663 live births in a study by **(Bonkowsky et a., 2010)** in Salt Lake City, Utah. Thirty types of leukodystrophies are described in literature with specific clinical characteristics and genetic causes. The inheritance patterns of the described LD are autosomal recessive (20 types), de novo dominant (8 types), x-linked recessive (1 type),

and x-linked dominant (1 type). These inheritance patterns strongly suggest LDs as monogenicity or Mendelian disorders. The most common types of LDs are metachromatic leukodystrophy, Canavan disease, Krabbe disease, Alexander disease, and x-linked adrenoleukodystrophy. Canavan disease is the most commonly diagnosed leukodystrophy among the patients in the current study, caused by mutation in ASPA gene. Although Canavan disease is a rare neurological disorder with an overall small number of patients worldwide, it had been reported in many Arab countries with the highest incidence among Saudi patients, with a clinical picture consistent with the classical clinical phenotype. Several mutations have been reported to circulate among Arab patients with no specific underlying or founder mutations. Most mutations were missense mutations followed by deletion mutations. The mutation distribution among Arabs seems to be different from other ethnic groups, which gives the CD Arab patients a distinct molecular profile, believed to be mainly due to the prevalent deep-rooted intra-familiar marriage culture. [(12)] The most common mutation reported in arab populations is missense mutation in exon 1 of the ASPA gene**.** [(5)] In 2013, **Di Pietro et al,** had reported two canavan disease Egyptian siblings of 4 years and of 4 months old. At four months of age, the clinical evaluation showed macrocephaly, hyperechogenicity of the white matter and thalamus, poor motility, no head control, and exophoria. Both Egyptian siblings were found to harbor a homozygous mutation in ASPA gene [(3)]. ASPA variants, which affect the ASPA enzyme function, were found in homozygous form among 11 Arab patients, mostly Saudias**.** [(14)] **MRI** done classify patients of leukodystrophies according to severity and distribution as showed in fig (1). In conclusion, we reported a large cohort of patients with leukodystrophies with different etiologies and inheritance pattern and create an algorithm hoping that others will find useful.

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