

AN OVERVIEW ON LEUKODYSTROPHY-A RARE BRAIN DISORDER

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ABSTRACT

Leukodystrophy is a group of metabolic and progressive disorder that genetically affects the central nervous system of the human body. Leukodystrophies are caused by abnormal development or destruction of the myelin sheath of the brain which is caused due to the specific gene abnormality. The lifespan of the patients depends on the age at which they are first diagnosed. The disease progresses more quickly when it is diagnosed at an early age. Currently, there is no cure for the leukodystrophies but stem cell therapy and bone marrow transplantation have each been tried in some cases and found to be successful. The benefits of transplant however, depend on the timing, age of onset and severity of symptoms. The damage caused to the white matter can lead to inflammation in the CNS, along with loss of myelin. The white matter destruction can be observed and leukodystrophy is diagnosed by MRI scanning. Leukodystrophy is generally characterized by specific symptoms including decreased motor function (inability to walk), muscle rigidity, and eventually degeneration of sight and hearing. Leukodystrophies has combined incidence and is estimated 1 in 7,600 of population. The inheritance of a recessive, dominant, or X-linked trait are involved while others, although involving a defective gene, are the result of spontaneous mutation rather than genetic inheritance. To study the cellular processes of myelination many research groups are implemented which provides insights into leukodystrophy and its related disorders. Researchers in New York have cured leukodystrophy successfully in mice, using skin cells to repair damaged myelin sheaths of the central nervous system.

KEYWORDS: Leukodystrophy, myelination, demyelination, diagnosis, treatment.**INTRODUCTION**

Leukodystrophy, a neurodegenerative disorder, is known to affect genetically to the central nervous system of the human body. It is caused as a result of abnormal development or destruction of the myelin sheath of the brain as a result, a change in white matter of the brain also occurs. The disease progresses more quickly if not diagnosed at an early age. The lifespan of the patients depends on the age at which they are first diagnosed. Currently, there is no cure for the leukodystrophies but stem cell therapy and bone marrow transplantation have been tried in some cases and found to be successful. The benefits of transplant, however depends on the timing, age of onset and severity of symptoms. The damage caused to the white matter can lead to inflammation in the CNS, along with loss of myelin. Leukodystrophy is generally characterized by specific symptoms including decreased motor function (inability to walk), muscle rigidity, and eventually degeneration of sight and hearing. It has been reported to occur 1 in 7,600 of the

human population. The disease is further subdivided into lysosomal, peroxisomal and mitochondrial diseases. In this study, we aim to discuss leukodystrophy with respect to its types, occurrence, symptoms, causes, diagnosis and also its treatment.

Types of Leukodystrophies

Leukodystrophy is classified into nearly 40 different type of which major types include the following:

1. Metachromatic leukodystrophy

This is a common autosomal recessive disorder caused by the deficiency of arylsulfatase, a lysosomal enzyme which is required for the metabolism of sulfatides, an important constituent of myelin sheath.^{[1][2]} It has various subtypes, some of which relate to the age when symptoms appear such as, late infantile MLD, juvenile MLD and adult MLD. In the infantile form, a loss of motor (movement) and verbal skill may be the first sign.^[3] Symptoms typically become progressively worse.

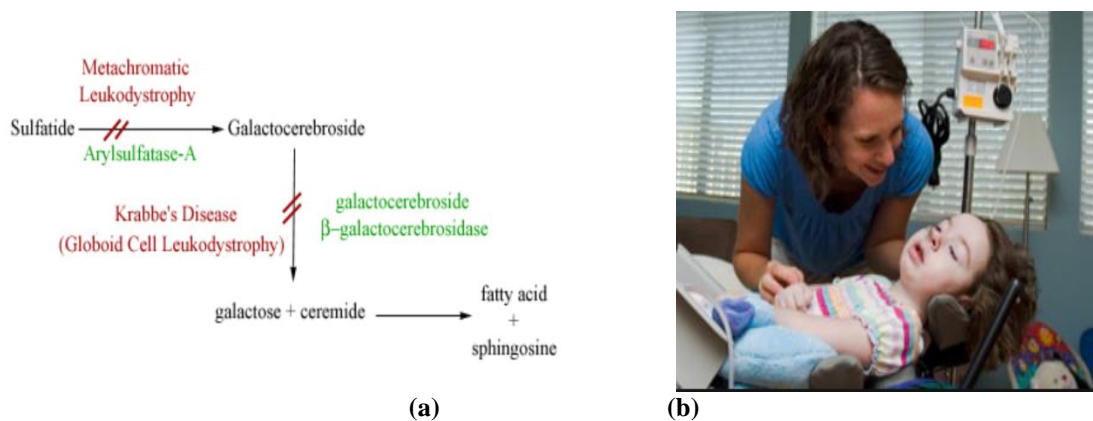


Fig. 1: (a) Shows the pathway of sulfatide metabolism (b) Shows a child suffering from MLD.

2. Krabbe disease

This is an autosomal recessive disorder that affects the myelin of the central and peripheral nervous systems caused due to deficiency of an enzyme, galactocerebroside (GALC) which causes degradation of galactolipids which are heavily present in the brain.^{[4] [5]} This degradation is due to presence of psychosine, a type of galactolipid which is 100 times more in the patient suffering with krabbe disease and is known to be the major reason responsible for its cause. It is also called as Globoid Cell Leukodystrophy since, a specific type of

cells called Macrophage accumulates high levels of undegraded galactolipids resulting in lack of GALC activity.^[6] About 90 per cent of those affected are babies, and symptoms usually show up before they are six months old. Some of the babies die at the age of 2 which occurs as a result of respiratory infection or brain fever.^[7] Other symptoms associated with infantile krabbe disease include; development delay, seizures, spasticity, optic atrophy, neurosensorial deafness, extreme irritability, ataxia and progressive psychomotor decline.

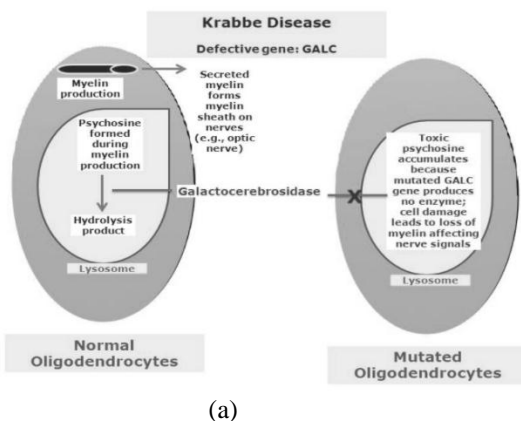


Fig. 2: (a) Shows the mechanism of krabbe disease (b) Shows a child suffering from Krabbe disease.

3. Canavan disease

Canavan disease is also called as spongiform leukodystrophy which is caused due to the deficiency of N-acetylaspartase. This results in accumulation of aspartic acid in urine, plasma and brain leading to

abnormal growth of myelin sheath.^[8,10] This disease is characterized by poor head control, decreased tone, regression and a markedly enlarged head. Eventually, the decreased tone changes to stiffness. Life expectancy is very limited.^[11,13]

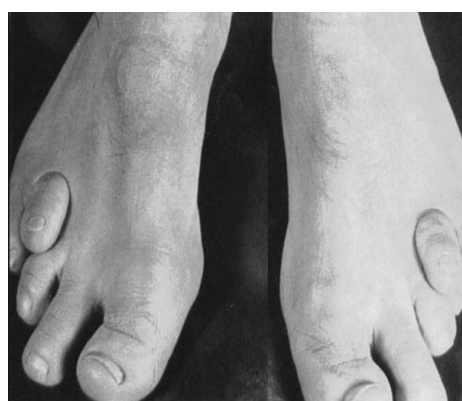


4. Adrenoleukodystrophy

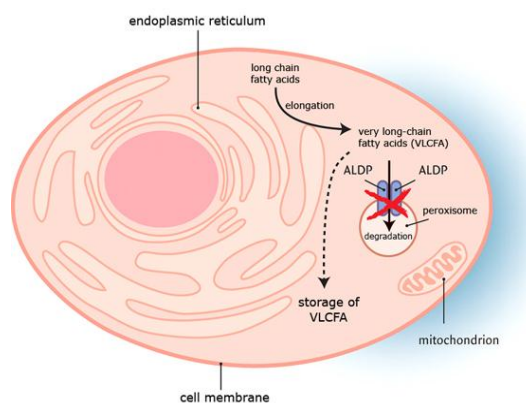
It is a rare peroxisomal disorder which affects the white matter of CNS, adrenal cortex and testes. It is due to genetic defect in X-linked gene located in Xq28 causing deficiency of an enzyme, acyl CoA synthetase, preventing the breakdown of very long chain fatty acids.^[14,16] The symptoms of the childhood cerebral form usually appear before 10 years of age and may progress rapidly with time. Adrenal glands of the patient are also affected, which indicate not enough cortisone is produced. Adrenomyeloneuropathy (AMN) is also caused by the same genetic change which is another form of X-linked adrenoleukodystrophy, where the patients generally have spinal cord dysfunction leading to difficulty in walking and changes in walking pattern. The spinal cord and the adrenal glands are affected by this dystrophy.^[17,19] Female carriers of the gene may show similar, but usually much milder, symptoms. In some, with the same genetic change, the adrenal gland may be

affected in isolation. Other symptoms such as Ataxia, hypertonia, seizures, adrenal insufficiency, sexual dysfunction, mild peripheral neuropathy and weight loss are also seen. Of the people suffering with AMN, 54% of the patients have normal brain function, where as 46% have brain involvement of varying degrees.

Another form of Adrenoleukodystrophy is the “Refsum disease” which is caused due to inability of the peroxisomes to break down phytanic acid present in the diet.^[19] The symptoms of this disease do not appear from birth and has normal growth. However, initial symptoms appear after the age of 20 or sometimes after the age of 50.^[20,21] Few symptoms of Refsum disease are: Retinitis pigmentosa, phariperal polyneuropathy, deafness, cerebral ataxia, anosmia (loss of smell), papillary abnormalities, shortening of the toe, Nystagmus (rapid, involuntary rhythmic eye movements), Ichthysis, Epiphuseal dysplasia.^[22]



(a)



(b)

Fig. 4: (a) Shows the image of patient suffering from “Refsum disease” (b) Shows the pathway by which ALD occurs.

5. Sjogren-Larsson Syndrome

It is caused as a result of mutation in a gene called fatty aldehyde dehydrogenase (FADH).^[23] FADH produces a gene responsible for breaking down molecules called medium and long chain fatty aldehydes.^[24] The

symptoms appear within first two years of life which include ichthyosis, mental retardation, seizures, speech difficulty, seizures, spasticity, glistening white dots in the retina of the eye, pruritis and preterm birth.^[25]



(a)



(b)

Fig. 5: Shows the image of patient with the symptoms of (a) Ichthyosis (b) Glistening white dots in retina.

6. Aicardi-Goutieres Syndrome

It is also called as familial infantile encephalopathy, is an inherited in an autosomal recessive manner where both

the parents of a child with aicardi-Goutieres syndrome carry a single copy of the defective gene responsible for the disease.^[26,27] The specific genetic defect involved in

the disease is yet to be identified. Therefore, the diagnosis of this disease is not possible. It is known to occur between 6-12 months of age and marked by the loss of acquired motor skills and spasticity. The disease is known to be progressive as per the age and 25% of the patients die before the age of 17 years.^[28,29] Some of the symptoms associated with the disease which may be

present are microcephaly, irritability, vomiting, dystonia, lack of progress of motor and social skills, ocular jerks, intracerebral calcification and sterile cerebrospinal fluid lymphocytosis. Skin lesions of the toes, fingers, puffy hands and feet may also be observed. However, all these symptoms are not present in all the cases.^[29]

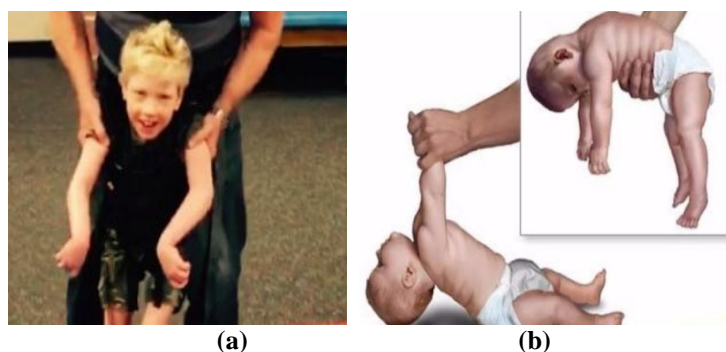


Fig. 6: Image showing the symptoms of (a) Calcification (b) Dystonia.

7. Alexander disease (AD)

It is divided into three different forms based on the age of onset and type of symptoms. They are infantile, juvenile and adult forms. This is not genetically inherited but is known to occur as a result of spontaneous mutation of a specific gene called Glial Fibrillary Acidic Protein (GFAP).^[30,32] In AD, Rosenthal fibres are found in astrocytes of glial cells which are generally absent in healthy people. These Rosenthal cells are known to contain large amounts of GFAP which causes the disease due to mutation in its sequence.^[33]

In Infantile Alexander disease, some children die in the first year of life where as a large number live for about 5-10 years of age. As the disease is progressive, it leads to severe mental retardation and spastic quadriplegia. Depending upon the severity of the disease, many symptoms are known to be observed such as; enlarged head circumference, feeding problem, hydrocephalus with increased intracranial pressure. Other symptoms

are; megalencephaly, failure to thrive, seizures, spasticity and progressive psychomotor retardation.^[34,35]

Juvenile Alexander disease is characterized by difficulty in talking, swallowing and inability to cough.^[36] Mental ability and head size remains normal and the age of onset is believed to be between the ages 4 and 10. Kyphoscoliosis (an abnormal curvature of the spine in both a coronal and sagittal plane) and other signs such as swallowing or speech difficulty, ataxia and spasticity are known to occur during the course of the disease.

Adult-onset Alexander Disease is the third form and is the rarest of all the forms and is believed to occur anywhere from late teens to very late in life.^[37] symptoms are similar to that of juvenile form and other symptoms resemble multiple sclerosis of tumour.^[38,39] This form of the disease is usually unnoticed until an autopsy is performed which reveals the presence of Rosenthal fibres.



(a)



(b)

(c)

Fig. 7: (a) Show the image of patient with the symptom of hydrocephalus (b) X-ray image of normal spinal cord (c) X-ray image of the patient with kyphoscoliosis.

8. Cerebrotendinous Xanthomatosis (CTX)

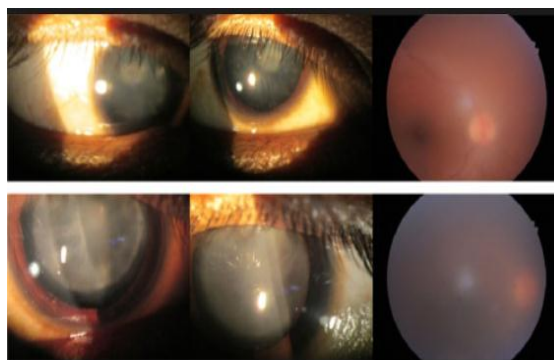
It is also called as Cerebral Cholesterinosis and is caused as a result of a mutation in a gene called CYP274A1 that produces an enzyme "sterol 27-hydroxylase" which is

responsible for converting cholesterol to bile acids.^[40,42] If it occurs to infants, symptoms such as Diarrhea, cataracts, psychomotor retardation and pyramidal/cerebellar spins are observed, where as in case

of adults, symptoms such as neurological dysfunction, mental retardation, cataract, optic disc paleness, premature retinal aging, xanthomas, premature arteriosclerosis, CAD, chronic intractable diarrhea, gall



(a)



(b)

Fig 8: Image showing the symptoms of (a) Osteoporosis (b) Optic disc paleness.

9. Vanishing White Matter Disease (VWMD)

It is a genetic disorder caused by mutations in one of the five genes EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5 that encodes the five subunits of a protein called eukaryotic initiation factor 2B (eIF2B).^[45,48] These genes are mandatory for the production of all other protein within the body. Therefore, any defect in one of these genes, causes decreased function of eIF2B and loss of function of the specific cells in the brain. It can also be inherited in an autosomal recessive manner where the carrier parents have a 25% chance of having the child affected by the disorder.^[49,50] Symptoms associated with this disease are; chronic neurological deterioration, febrile episodes, cerebellar ataxia, spasticity, seizures, ovarian dysgenesis in female patients, lethargy, coma and sometimes death.

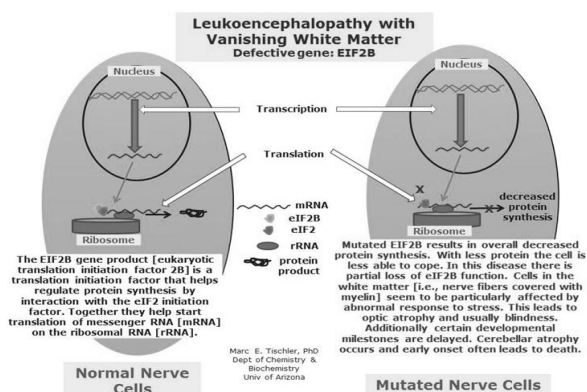


Fig. 9: Image showing the pathway of vanishing white matter disease.

10. 4H syndrome

It is an abbreviation for hypomyelination (lack of myelin sheath in the CNS), hypogonadotropic hypogonadism (absence of normal puberty development) and hypodontia (absence of all teeth).^[51,52] It is an autosomal recessive inherited disease; however, its genetic basis is still under study and is not completely known.^[53] The disease is associated with several neurological symptoms

stones, osteoporosis, Epileptic seizures, EEG abnormalities and psychiatric symptoms such as hallucinations, aggression, depression and suicide attempts are observed.^[43,44]

such as late walking, early-onset ataxia, deterioration of ataxia, slow progression of ataxia over time, dysarthria, spasticity and rarely seizures.



Fig. 10: Image showing the symptom of hypodontia.

There are other types of leukodystrophies which are not described since their occurrence is very rare, they are:

- ✓ Acute Disseminated Encephalomyelitis (ADEM)
- ✓ Adult Onset Autosomal Dominant Leukodystrophy (ADLD)
- ✓ Adult Polyglucosan Body Disease
- ✓ Fucosidosis
- ✓ Fukuyama Congenital Muscular Dystrophy
- ✓ Galactosialidosis
- ✓ Tay-Sachs Disease
- ✓ Nasu Disease
- ✓ Zellweger syndrome

Diagnosis

The destruction of the myelin sheath can be observed in a basic MRI scan and is used to diagnose all types of leukodystrophies.^[54] When a leukodystrophy is suspected, the brain MRI becomes a crucial tool to formulate a diagnostic hypothesis. The first distinction to make when looking at the MRI is whether the white matter abnormalities correspond to a demyelinating or hypomyelinating process.^[55,57] Demyelinating is characterised by prominent hyperintensity of white

matter whereas in hypomyelinating, the white matter abnormalities appears mildly hyperintense.

Oftentimes, doctors have to use several types of testing, including:

1. Blood and urine analysis
2. CT scans
3. Genetic testing
4. MRI scans
5. Psychological and cognitive tests.^[8]

Leukodystrophy present in an individual is diagnosed by the following series of processes:

1. Obtaining a medical history and detailed family history.
2. Performing a physical examination and neurologic examination.
3. Review of brain MRI findings:
 1. T₂-weighted hyperintensity in the white matter is the MRI finding required for diagnosis of a leukodystrophy.
 2. T₁-weighted signal may be variable: iso- or hyperintense signal of T₁- weighted is consistent with a hypomyelinating type whereas hypointense T₁-weighted signal is consistent with a demyelinating leukodystrophy.

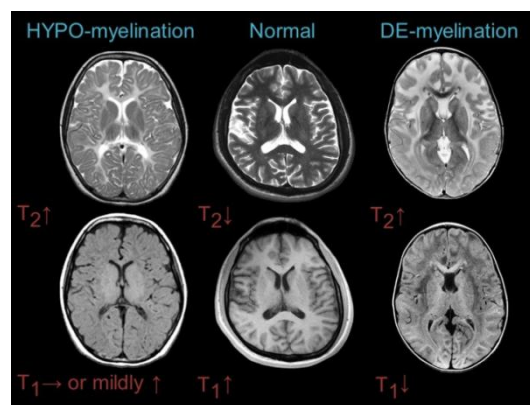


Fig. 11: MRI images showing the intensities of white matter.

4. Performing specialized laboratory testing, often including molecular genetic testing (either stepwise single gene testing or use of a multi-gene panel targeted to the leukodystrophies).^[58]

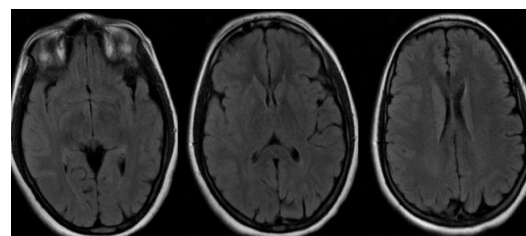


Fig. 12: MRI scans of normal brain.

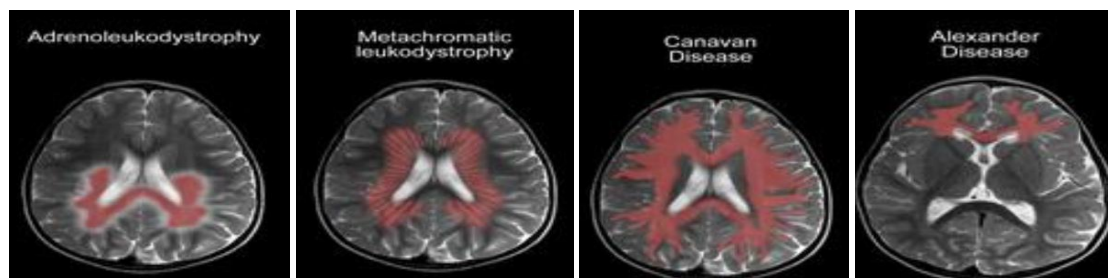


Fig. 13: MRI scans of some of the leukodystrophies with the affected (coloured) areas in the brain.

Treatment

Treatment therapies vary with many different types and causes of leukodystrophy. Many studies and clinical trials are in progress to find better treatment and useful therapies for each of the different leukodystrophies. Stem cell transplants^[59] and gene therapy^[60] appear to be the most promising treatments in treating almost all types of leukodystrophies but it should be done as early as possible after diagnosis of the disease. For hypomyelinating leukodystrophies, therapeutic research is done into cell-based therapies which appears promising. Oligodendrocyte precursor cells and neural stem cells have been transplanted successfully and have shown to be healthy even after an year. Fractional anisotropy and radial diffusivity maps showed possible myelination in the region of the transplant. Induced pluripotent stem cells, oligodendrocyte precursor cells, gene correction and transplantation are done to promote the maturation, survival and myelination of

oligodendrocytes and these seems to be the primary routes for possible treatments. Different therapies for the treatment are described below.

1. Stem cell transplant
2. Gene therapy
3. Genetic counselling
4. Medications used for seizures

i. Stem cell transplant

The only treatment (therapy) at present is a stem cell (SCT) or bone marrow transplant (BMT). But today's successful stem cell or bone marrow transplant (BMT) is not a complete cure but it slows further deterioration by replacing the effected marrow with healthy marrow that can produce the missing enzyme. Today's transplants do not reverse the damage that the brain has already experienced so they are most successful when there is little or no damage. The transplant teams are working hard to try to minimize the conditioning, which has

traditionally some sort of chemotherapy to kill off the existing bone marrow.^{[59] [61,62]}

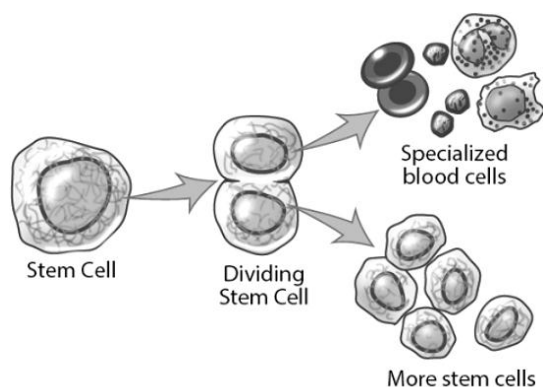


Fig. 14: Image showing the division of stem cells to be used in the treatment.

ii. Gene therapy

This is a procedure involving the insertion of a normal gene into an organism in order to achieve a therapeutic objective.^[63] This gene (transgene) can be the normal version of a defective gene causing disease or a gene that produces a protein with any therapeutic action. Here the gene responsible for making a protein is dystrophin. Mutations in the human dystrophin gene cause leukodystrophies. These are treated by gene knockout. Knockout gene is a process which involves deleting a gene or disrupting a gene's function in a mice organism.^[64] For example, Metachromatic Leukodystrophy (MLD) is caused by genetic deficiency of Aryl sulfatase A enzyme. Failure in catalysing the degradation of sulfatide leads to demyelination in peripheral and central nervous system. The ARSA knockout mice develop a disease that resembles MLD but is milder.^[65]

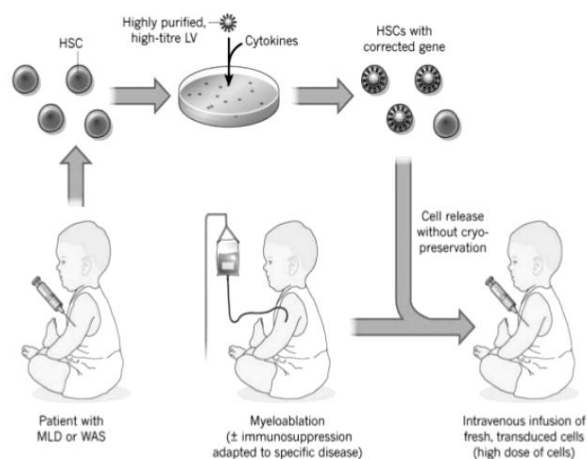


Fig. 15: Image showing gene transfer therapy to treat MLD.

iii. Genetic counselling

Genetic counselling is the process of advising and counselling the patients or relatives who are at risk of an inherited disorder by making them aware of the

consequences and nature of the disorder, the probability of developing or transmitting it, and the options which are open for them in management and family planning. Some types of leukodystrophies have an identified genetic cause which is either inherited in a dominant manner, recessive manner of an autosomal gene, or an X-linked recessive manner. Genetic counselling regarding risk to the family members mainly depends on accurate diagnosis, determination of the mode of inheritance in each family, and the results of molecular genetic testing. Prenatal testing is done in pregnancies which are at higher risk of developing some types of leukodystrophies if the pathogenic variant(s) in the family are known. Many leukodystrophies are still with an unidentified genetic cause and once a genetic cause is identified, other inheritance patterns may emerge.^[58]

iv. Medications

For the treatment of leukodystrophies there are no such medications used. But the anti-epileptic and anti-convulsant drugs are used to curb the symptoms of leukodystrophy. Some of these medications include:

- Acetazolamide
- Carmustine
- Carbamazepine
- Nitrazepam
- Pregabalin

Acetazolamide

It is a sulfonamide derivative with diuretic, antiglaucoma and anticonvulsant properties. The mechanism of action of acetazolamide is as a Carbonic Anhydrase Inhibitor so its antiepileptic effect is due to its inhibitory effect on brain carbonic Anhydrase. This leads to an increased transneuronal chloride gradient, increased chloride current, and an increased inhibition.^[66,68]

Carmustine

These are compounds that have nitroso (R-NO) group and a urea. Hence, come under the class of nitroureas. They have little cross resistance with other alkylating agents. Drugs like carmustine, lomustine can easily cross blood-brain barrier. So they are used to treat brain disorders.^[69,70]

Carbamazepine

It is a tricyclic compound chemically related to tricyclic antidepressants (TCA) with anticonvulsant and analgesic properties. The mechanism of action of carbamazepine is as a Cytochrome P450 inducer. Carbamazepine exerts its anticonvulsant activity by reducing polysynaptic responses and blocking post-tetanic potentiation.^[70,73]

Nitrazepam

It belongs to a group of medicines called benzodiazepines. It acts on benzodiazepine receptors in the brain which are associated with the GABA receptors (gamma amino butyric acid). GABA acts as a major inhibitory neurotransmitter in the brain which is involved

in inducing sleepiness, relaxation of muscles and control of anxiety, depression and fits.^[74,76]

Pregabalin

It is a 3-isobutyl derivative of gamma-amino butyric acid (GABA) with anti-convulsant, anti-epileptic, anxiolytic and analgesic activities. Pregabalin selectively binds to alpha2delta (A2D) subunits of presynaptic voltage-dependent calcium channels (VDCCs) located in the central nervous system (CNS). Pregabalin is an inhibitor of neuronal activity used for therapy of neuropathy.^[77,78]

Treatment depends on the type of leukodystrophy. Many of the drugs are under clinical trials in order to find the treatment and therapies for different leukodystrophies. Lorenzo's oil, which is a mixture of two oils (Glycerol trierucate and glycerol trioleate) is commonly used to normalize the fatty acid levels in case of adrenoleukodystrophy^[79,82], but, its activity is unclear if it can prevent progression prior to onset of brain involvement.^[83,84] However, stem cell transplants and gene therapy appear to be the most promising in treating almost all types of leukodystrophies unless performed in the early stages.^[59,60]

Researches

A Foundation was established for studying Metachromatic Leukodystrophy which provides updates on MLD research, including (as of 2017) three clinical trials as it evaluates therapies related to gene and enzyme replacement and various lines of basic research. They are also active in newborn screening.

The Global Leukodystrophy Initiative was formed in 2013 to bring together clinicians, researchers and advocacy groups to focus and improve both clinical care and research.

Many research groups have been studied to understand the cellular processes of myelin growth and which provides the insights into leukodystrophies. Researchers in New York have successfully cured leukodystrophy in mice, using skin cells to repair damaged myelin sheaths. Researchers have hypothesized that the treatment by stem cell transplant may possibly be used in curing human multiple sclerosis also.^[22]

CONCLUSION

Leukodystrophy is a brain disorder that effects the white matter of the brain called the myelin sheath which insulates the central nervous system. It causes loss of normal voluntary and involuntary functions of the brain like movements of limbs, hearing loss, difficulty in speech etc. This article provides the detailed information regarding the brain disorder called as leukodystrophy. Most of the leukodystrophies are inherited that means they are passed down through family genes to their offsprings. In some they may not be inherited, but are

still caused by a genetic mutation that is rapid change in the genes.

The onset of symptoms are variable depending upon the type of disorder. Some specific symptoms vary from one type of leukodystrophy to the next but the vast majority of symptoms are shared as the causes for the disease generally have the same effects. Symptoms mainly depends on the age of onset, which is predominantly in infancy and early childhood, although the exact time of onset may be difficult to determine.

There is no complete cure for leukodystrophies till date, but supportive treatment can help manage and curb some of the symptoms. The insights into the histopathological and cellular consequences of sulphatide storage have been provided by the knock-out mouse model of MLD.

Because of the inheritance pattern of X-linked diseases, males are more often affected by this type of leukodystrophy, although female carriers are often symptomatic, though not as severely so as males. Till today, no cases of a leukodystrophy have been found in which the effected gene is carried on the Y chromosome.

Once a leukodystrophy is considered in an individual, the following approach can be used to determine the specific leukodystrophy to aid in discussions of prognosis and genetic counseling. Certain clinical features are required to know the history of the patient as they may be helpful in identifying a specific leukodystrophy. However, in the majority of cases, only nonspecific loss of function occurs that are primarily motor functions and medical history alone does not provide insight into a specific diagnosis.

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