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A Detailed Review on Insights of Canavan Disease: A White Matter Disorder Encloses With Etiology, Pathophysiology, Diagosis, Treatment

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ABSTRACT
Canavan disease (CD), a rare recessive autosomal genetic disorder, is distinguished by an early onset and a progressive spongy degeneration of the brain characterised by loss of the axon's myelin sheath. Following a relatively normal birth, homozygous individuals typically develop clinical symptoms within months and die within several years of the disease's onset. A biochemical defect associated with this disease reduces the activity of the enzyme N-acetyl-L-aspartate amidohydrolase (aspartoacylase), and affected individuals have a reduced ability to hydrolyze NAA in brain and other tissues. Children with neonatal/infantile-onset Canavan disease frequently become irritable and have sleep disturbances, seizures, and feeding difficulties as they grow older. Swallowing becomes increasingly difficult, and some children require nasogastric feeding or permanent feeding gastrostomies. Joint stiffness worsens, and these children resemble people with cerebral palsy. The present review article take a overview on the basic information along with the Etiology, Pathophysiology,Diagnosis and Treatment which is available for the canavan disease.

Key Words: Canavan Disease, Etiology, Pathophysiology, Diagnosis, Treatment.

I. INTRODUCTION

A childhood leukodystrophy known as Canavan illness frequently results in infant mortality. Its origin can be traced to Myrtelle M. Canavan, who in 1931 wrote a case study about a young infant with a greatly enlarged head, neurological symptoms like nystagmus, and psychomotor impairment (1). It is rare, fatal neurological hereditary condition, also known as Canavan-Van Bogaert-Bertrand disease, first manifests in infancy. It belongs to a class of hereditary disorders known as leukodystrophies. It is linked to a lack of a key enzyme that causes the loss of white matter in the brain, which then results in poor nerve signal transmission. (2)(3)

The newborn variety is the most prevalent and frequently has the most serious symptoms. Most newborns seem healthy right away, but by two to six months, gross motor development impairments become clear. It's possible that the baby won't be able to move, turn over, control its head, or stand up by itself. A common symptom that is frequently linked to macrocephaly is hypotonia. Most babies struggle to eat and start having seizures. (4)(5).

White matter dysmyelination, which is characterised as spongy degenerations, is the main symptom of Canavan's disease, which is a deadly condition that first manifests in early infancy. Canavan's illness is notable for its failure to meet neurodevelopmental milestones, unusually low muscle tone, enlarged head size, seizures, atrophy of the optic nerve, and early death. (6)(7)(8)(9).

A spongiform leukodystrophy with an autosomal recessive inheritance is Canavan disease. (10)(11). The Ashkenazi Jewish population is more likely to contract this disease, but cases in non-Jews are also becoming more common. However, the disease's frequency and presentation in India are largely unknown; for this reason, we are reporting this series. (12)(13)

ETIOLOGY

Aspartoacylase (ASPA) gene disruptions or modification (mutations) are responsible for Canavan disease. This mutation is inherited as an autosomal recessive condition. Canavan disease is also referred as spongy degenerate because it causes a spongy degeneration of the white matter in the brain to victims. Mutation in the ASPA gene lead to a deficiency in aspartoacylase (aminoacylase 2), which catalyses the hydrolysis of N-acetylaspartate, and are the cause of Canavan disease, an autosomal recessive trait of inheritance (NAA). (14)

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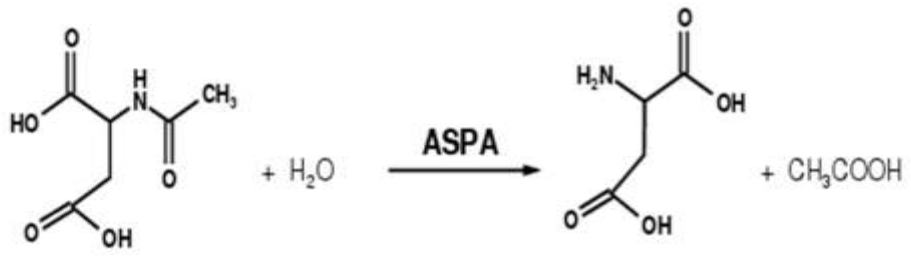

Figure 1: Aspartoacylase (ASPA) catalyses the hydrolysis of N-acetyl aspartic acid.

The interaction of the genes of the genes for a specific trait that are on the chromosomes received from the mother and father determines the presence of genetic illnesses. When person receive the same defective gene for the same trait from both parents, recessive genetic diseases develop. A person will be a carrier for the disease if they have one normal gene and one sick gene, although they won't exhibit any symptoms. With each pregnancy there is a 25 % chance that two carriers may carry the faulty gene to their offspring and cause them to be ill. With each pregnancy, there is a 50% chance that the child chid will carry the same gene as one of the parents. A child has a 25% probability of inheriting normal genes from both parents and being genetically normal for that specific trait. Both men and women are at the same level of danger. On chromosome 17, a faulty gene that cause Canavan illness has been identified. Human cells contain chromosomes, which house the genetic material that makes each person unique. 46 chromosomes typically make up human body cells. The sex chromosomes pairs are numbered from 1 to 22. Females have 2 X chromosomes and one Y chromosomes, while males have one X and one Y chromosomes. The short arm of each chromosome is denoted P and the long arm is designated q. Chromosomes are further separated into numerous numbered bands. Band 13 on the short arm of chromosome 11, for instance, it is referred as chromosome 11p13. The numbered band indicate where the hundreds of genes found on the. An enzyme that degrades (metabolises) N-acetylaspartic acid is called aspartoacylase, and the ASPA carries instructions for creating (encoding) it (NAA). NAA is a substance that scientists think essential for preserving the white matter of the brain. NAA builds up in the brain tissue as a result of insufficient or inactive aspartoacylase. Canavan disease symptoms are caused by brought on by excessively high NAA levels. (15)(16) It is brought on by a mutation in the aspartoacylase-encoding ASPA gene. As a result of this mutation, aspartoacylase is deficient and N-acetyl aspartic acid (NAA) builds up in the brain. In the phospholipid layer of axons, myelin degradation and oligodendrocyte dysfunction are thought to be caused by NAA (17).N-acetylaspartate (NAA), despite having an unclear physiological role, is frequently utilised in magnetic resonance spectroscopy as a diagnostic of neuronal integrity (18).In fact, NAA is one of the most prevalent organic metabolites in the mammalian brain and exhibits a remarkable degree of segmental metabolism, with CNS concentrations in the millimolar range. In neurons, N-acetyltransferase 8-like (NAT8L) synthesises NAA from acetyl-CoA and aspartate, whereas in oligodendrocytes, aspartoacylase (ASPA) hydrolyzes NAA into aspartate and acetate (19).

According to clinical data, modifications to NAA metabolism are not well tolerated. NAA production is abolished when NAT8L activity is lost, and this has been associated with the neurodevelopmental condition. Hypoacetylaspartia with seizures, ataxia, and microcephaly as symptom (20). Conversely, leukodystrophy Canavan disease (CD), characterised by an accumulation of NAA in the brain, blood, and urine, is brought on by a lack of NAA catabolism brought on by missense mutations in the ASPA gene. Patients with CD, a fatal neurodegenerative condition in which they do not meet developmental milestones, exhibit macrocephaly, seizures, widespread CNS vacuolization, and hypomyelination. (21)(22). Due to its catastrophic

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effects and lack of available treatments As an experimental treatment for CD patients, ASPA gene substitution therapy has been tried. (23).

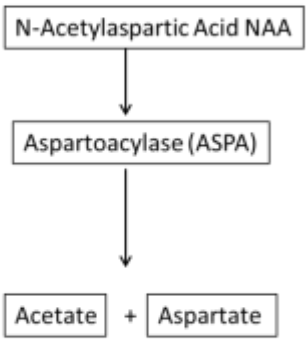
Although the first-generation viral vectors used in the experimental clinical treatment were safe, the therapeutic results were only moderate. Recombinant adeno-associated virus (AAV) vectors with cell type-specific tropism or the capacity to cross the blood-brain barrier have been used in ASPA gene replacement studies. Novel gene therapy options that meet the needs for treating CD are now becoming available. (24).

Up to three months of age, CD can be avoided by delivering the ASPA gene directly to the neonatal mouse brain using an oligodendrotropic AAV vector. (25)

Additionally, a CD mouse model has demonstrated the value of ectopic NAA sinks in neurons or astrocytes created using cell type-specific AAV-ASPA vectors. (26)(27).These studies suggest that ASPA expression in any of the major CNS cell types can result in neurological improvements, at least in mice, a species with a comparable short lifespan. It will be possible to better understand the pathophysiology of CD and determine the best target tissues for gene therapy by determining the function of ASPA cell types and tissues. There is no doubt that ASPA is abundantly expressed in the CNS's oligodendroglia, but rats have also shown that it is also expressed in neurons and microglia. (28)(29)(30)

A recent study found CD mice had impaired immune function and that ASPA is widely expressed in peripheral organs (31). Demonstrating the need for a deeper comprehension of extra-cerebral ASPA's role in determining the main target tissue for treatment. Preclinical gene therapy research and findings from ASPA double-knockout mice show that excess NAA causes toxicity rather than a deficiency in NAA-derived acetate that results in hypomyelination as the aetiology of CD. (32)(33)(34)(35).N-acetyl-aspartate, a highly concentrated brain neurotransmitter, is broken down by the aspartoacylase enzyme, which is responsible for Canavan disease.the gene causing Canavan's disease, a condition that causes the white matters of the brain to be destroyed, has been discovered, adding to our understanding of genetic problems involving myelin (36). Aspartoacylase deficiency and N-acetyl aspartic acid build up in the brain are the cause of Canavan disease, an autosomal recessive leukodystrophy (37). Unexpected mutation in the ASPA gene is the root cause of Canavan illness. This gene is in charge of producing the aspartoacylase enzyme. N-acetyl-L-aspartic acid, which is mostly present in the brain, is broken down by aspartoacylase (NAA). Because of mutation in the ASPA gene, aspartoacylase is less able to degrade NAA, which result in the molecule accumulating in the brain, notable in brain cells (neurons). NAA builds up in nerve cells when enzyme activity is diminished or absent (ineffective), which damage both the individual nerve cells and the surrounding nerve tissue. For myelin to grow and stay healthy, NAA is thought to be crucial. The sheath or covering known as myelin coast, shields, and insulates nerve fibres. The nerves are unable to function properly when myelin is destroyed, a process know as demyelination. Nerves are used by the brain to communicate with the body. Demyelination impairs the brain's ability to efficiently communicate with other parts of the body. This causes a steady decline in neurological function. (38)

Metabolic Process of Healthy N-Acetylaspartic Acid NAA



Normal Neuron

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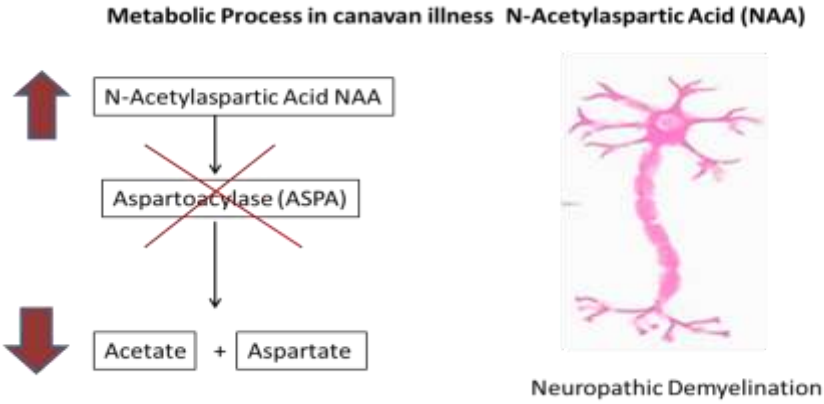

PATHOPHYSIOLOGY

NAA is derived from aspartic acid and acetyl-CoA. The second-most prevalent free amino acid in the brain, according to some estimates, is this one. It is present in neurons where it is produced by mitochondria and then transferred to oligodendrocytes via axo-glial contact zones. Between the innermost oligodendrocytes plasma membrane and the axonal membrane, these axo-glial contact zones are connected. N-acetylaspartylglutamate (NAAG) is produced by the conversion of NAA inside neurons. Following its transit, it is hydrolysed into NAA and glutamate by astrocytes. By oligodendrocytes, which are where aspartoacylase is primary found, the NAA is finally absorbed.

When NAA is converted to aspartate (aspartic acid) and acetate, the aspartoacylase enzyme is responsible. Because of this, NAA builds up in the brain when this catalyst is lacking.

The patient's plasma, urine and CSF fluid all have noticeable higher levels of NAA. Aspartoacylase deficiency is fundamentally characterised by abnormal myelination and the accompanying conspicuous swelling and vacuolated astrocytes. The term spongiform leukodystrophy refers to these outcomes. To what extend accumulated NAA contributes to the aetiology of this spongiform degeneration is still unknown. (39)

Possible pathological mechanism responsible for CD

It has been discovered that N-acetylaspartic acid is only generated in neurons and has been isolated from mitochondrial and microsomal fractions.(40) Transporters move NAA and its associated dipeptide N-acetyl-aspartyl-glutamate (NAAG) from the cytoplasm to the extracellular space. Additionally, oligodendrocytes take up NAA through a dicarboxylic acid transporter before it is degraded by ASPA.

As a clinical indicator of the brain's neuronal metabolic integrity, N-acetylaspartic acid is used. Because CD is associated with elevated NAA levels in the brain, it differs from many other neurodegenerative disorders in which a drop in NAA has been recorded. Additionally, patients with a Pelizaeus-Merzbacher-like condition, which is characterised by the loss of myelin, have shown a notable increase in NAAG concentration.(41)The specific role of NAA in the development of the central nervous system (CNS) is still understood, but it is crucial to understand why increases in NAA or NAAG cause white matter degradation or dysmyelination.

To explain the pathophysiology of CD in the CNS, various theories have been put forth.

First, demyelination might be a result of NAA's direct interaction with oligodendrocyte NMDA receptors. However, in a rat research, NAA did not induce any current in oligodendrocytes. Therefore, it is doubtful that the action of NAA or NAAG on oligodendrocyte NMDA receptors will play a significant role in the development of white matter injury.(42) The second possibility is that NAA can be hydrolyzed by ASPA into acetate and aspartate, acting as a molecular water pump to remove metabolic water from mitochondria and neurons. According to this theory, NAA buildup causes CD to experience astrocytic edoema and the development of vacuoles.(43)But according to a prior study, NAA was safe even at high concentrations.(44)despite NAA levels falling due to the production of a normal ASPA gene that was inserted, CD mice showed no signs of improved functionality.(45) Aquaporin 4 (AQP4) was found everywhere over the cytoplasm of CD animals, while it was only found in the astrocytic end-feet of

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control mice, according to an immunohistochemistry investigation using the Nur7 mouse model of CD. This suggests that AQP4 may be a potential CD therapeutic target and that the management of water homeostasis by astroglia may contribute to the partial prevention of spongy degeneration.(46)

Thirdly, during the process of postnatal myelination in the CNS, NAA may be crucial for lipid production and myelination.(47) Increases in NAA and a decrease in acetate and aspartate are two characteristics of CD.(48)(49) Thus the loss of ASPA function may be associated with a decrease in the amount of free acetate available for the synthesis of lipids. Spongiform degeneration has been linked to NAA's inability to transport acetate from the mitochondria to the cytosol in CD brains, which impairs lipogenesis.(50)(51) A reduction in acetyl groups in the absence of ASPA activity may therefore be one of the primary causes of CD. While other lipids were not significantly changed, non-polar and polar lipid levels, which are essential for the formation of myelin, were discovered to be significantly lower (21-38%) in ASPA knockout mice than in wild type.(50) Additionally, both in the rat CD model and in human CD patients, a reduction of cerebroside and sulfatide, component glycolipids of myelin in the white matter, was noted. The clinical severity of the condition may not have directly connected with the observed fall in lipid levels, though. These findings imply that acetate shortage is not the only factor contributing to CD aetiology.

Fourth, NAA might be crucial in preserving the metabolic stability of oligodendrocytes. It has been demonstrated that an increase in oxidative stress markers occurs before oligodendrocyte loss and demyelination in the early postnatal period.(52) Despite the fact that NAA is largely generated and concentrated in neurons.(53) In addition, young oligodendrocytes have been found to have elevated NAA concentrations. But neither mature oligodendrocytes nor astrocytes were found to contain NAA, suggesting that ASPA serves a critical role in immature oligodendrocyte development.(54) Non-myelinated oligodendrocytes have been shown to express ASPA mRNA and protein in rat cortical cells, as well as to exhibit ASPA activity.(55)(56) Even though oligodendrocytes have not yet been shown to directly absorb NAA, axonal transport of NAA has been proven.(57) According to these results, myelin maintenance is compromised when NAA-derived acetate is not present. In addition to being demonstrated to contribute to the pathogenesis of CD, ASPA is essential for the maturation of oligodendrocytes.(58) Additionally, in a mouse model of adult ASPA deficiency, changes in the control of the cell cycle, the acetylated status of nuclear histones, ongoing neurogenesis in neural cell progenitors, and a significant decrease in certain myelin proteins have been noted.(59)

Hypotheses on the pathogenesis of CD

Due to our ignorance of the precise pathophysiological pathways connecting the documented ASPA mutations to the diverse clinical presentation of CD, a number of ideas have been made in an effort to explain how the absence of ASPA activity causes the neurodegeneration and oedema seen in CD. One of them, the "Ac-lipidmyelin" theory, states that a lack of NAA-derived Ac prevents the production of myelin lipid.(60)Despite the fact that acetyl moieties from NAA have been shown incorporated into myelin lipids(61)

It is thought to be involved in myelination but is not required for it, according to evidence of rare cases of CD in which ASPA is dysfunctional but myelination still continues normally.(62)(63)It is important to keep in mind, though, that experimental data indicates that oligodendrocytes are the primary cell type in which ASPA is expressed.(64) indicating that myelination in the central nervous system closely coincides with the development of the ASPA gene's expression pattern in the postnatal rat brain.(65)

Another theory, known as the "osmotic-hydrostatic" hypothesis, contends that the movement of NAA between brain cells functions as a molecular water pump, drawing metabolic water out of neurons.(66)A cation and 32 water molecules form a compound with NAA when it is generated.(67)This NAA complex has been demonstrated to be released by depolarized neurons in grey matter into the extracellular fluid (ECF), carrying water against its gradient.(68)This complex quickly diffuses into the oligodendrocytes in a healthy person, where it passes through hydrolysis and releases water molecules.(69)Then, when its concentration gradient decreases, this free water diffuses into the vascular system.(70)On neuronal depolarization, the NAAwater complex is still produced in CD patients, but it is not removed from the ECF and instead diffuses into the vasculature (which has restricted permeability to hydrophilic molecules)(71)Local osmotic pressure adjustments may result from the NAA-water

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complex accumulation in the ECF. The ensuing alterations in osmotic pressure could explain the osmotic diseases associated with CD if a comparable NAA cycle disturbance takes place in white matter.(60)Although the release of NAA into the ECF as a result of depolarization of white matter neurons has not been shown, it has been proposed that N-acetylaspartylglutamic acid (NAAG) produced by neurons may act as a source of NAA in this situation.(60)It is thought that white matter oligodendrocytes obtain NAA from NAAGpeptidase, which is found in the astrocyte end foot at the nodes of Ranvier and hydrolyzes NAAG to create NAA.The limited extracellular space at nodes in white matter, on the other hand, means that any potential failure of oligodendrocyte removal of NAA and its subsequent accumulation will probably have severe osmotic consequences, which could account for vacuole formation and the observed splitting between myelin sheath layers.(60)

A third theory that was just recently put up by Francis et al.(72)oxidative stress in myelinating oligodendrocytes as a result of disruption to NAA catabolism during crucial myelination phases in early development leads to dysmyelination and other CD-related diseases. In this "oxidative stress" concept, NAA is proposed to lessen oxidative stress by avoiding the linkage of fatty acid production to oxidative energy metabolism through the availability of Ac. The latter can be changed by the enzyme acetyl-coenzyme A synthetase into acetyl-coenzyme A (Acetyl-CoA). In nur7 mouse models, oxidative stress was demonstrated to occur before dysmyelination.(72)And even more recently, Francis et al. corroborated this theory by demonstrating that injection of triheptanoin (which raises Krebs cycle intermediates) reduces oxidative stress and alleviates CD-related diseases.(73)

Table 1 : Overview of the three current ideas for Canavan disease's (CD) pathophysiology, their underlying mechanism(s), and potential neuroprotective measures for each.

Hypothesis	**Outline of the mechanism(s) and potentialneuroprotectant(s)**
Ac-lipid-myelin	➢ NAA-derived compounds are lacking in CD patients. Ac prevents oligodendrocytes from synthesising myelin lipids. ➢ Possible therapy strategy: CA, GTA
osmotic-hydrostatic	➢ NAA cycling serves as a molecular water pump in brain cells. ➢ Patients with CD have variations in local osmotic pressure as a result of the NAA-water complex building up in the ECF. ➢ A potential failure of oligodendrocyte removal of NAA (and its subsequent build up) in the white matter of CD patients may have severe osmotic consequences because of the limited extracellular space at nodes, which could account for vacuole formation and the observed splitting between myelin sheath layers. ➢ Pyrazole and its derivatives, sodium valproate, topiramate, ethanol, LiCl, Li3C6H5O7, and NAA are examples of possible treatment agents.
oxidative stress	➢ When NAA catabolism is disrupted in CD patients, it leads to oxidative stress in myelinating oligodendrocytes, which leads to dysmyelination and other CD-related diseases. ➢ Lipoic acid and triheptanoin are two potential treatment options.

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DIAGNOSIS

The first 3 to 6 months of infancy are often when symptoms first show, and they progress quickly. These signs may manifest as –

1) Poor head control
2) Abnormally large head
3) Lack of motor development
4) Hypotonia – decreased muscle tone
5) Blindness
6) Seizures
7) Difficulty swallowing
8) Unresponsiveness
9) Lethargy
10) Irritability
11) Feeding difficulties
12) Paralysis
13) Hearing loss
14) Sleep disturbance
15) Hyperextension of legs
16) Flexion of the arms
17) Megalocephaly
18) Nasal regurgitation
19) Reflux with vomiting
20) Mental retardation

There is wide range of Canavan illness severity. All are wont experience all of symptoms due to the varying Degree and symptoms. Neuroimaging and clinical characteristics are particularly useful and specific for Canavan disease (74). The white matter of the cerebral hemispheres and the cerebellum frequently exhibits diffuse hypodensity on a CT scan, with the globus pallidus typically involved and the caudate nucleus and putamen spared. The leukodystrophy visible on a cranial MRI progresses centripetally, involving subcortical U-shaped white matter fibres first and then central regions. Usually, just the thalamus and globus pallidus are affected, sparing the putamen and caudate nucleus (75).Later stages entail diffuse, extensive white matter involvement and lateral ventricle enlargement. Traditionally, cultivated skin fibroblasts are used in an enzyme assay (Aspartoacylase enzyme) to diagnose Canavan disease (76). The diagnosis is made when there are elevated levels of urine NAA in babies who have symptoms, consistent clinical characteristics, and neuroimaging results that indicate aspartoacylase deficiency. Clinical traits such hypotonia, weak head control, and macrocephaly are compatible. Defective aspartoacylase activity in cultivated skin fibroblasts can be used to make a more precise determination. Genetic testing is only requested for genetic counselling if increased urine NAA and skin fibroblast testing are diagnostic. (77)(78)(79). A devastating condition known as CD affects both the white and grey matter of the central nervous system. (80). The pathognomonic biochemical indicator of CD is the build-up of NAA in the blood, urine, CSF, and amniotic fluid. Numerous studies and hypotheses have addressed the part that NAA accumulation plays in the pathogenesis of progressive myelin degeneration in CD (81)(82)(83).The molecular efflux water pump mechanism, which obeys a transport gradient between two juxtaposed anabolic (neurons) and catabolic (oligodendrocytes) compartments, is thought to involve NAA and, particular in, ASPA. Absence of ASPA activity results in the vascular spongiform degradation of grey matter and existing myelin, as well as excessively high osmolar levels in the peri axonal region. The white matter has a significantly higher water content. (84).

This explains why macrocephaly with CD is caused by megalencephalic with elevated cerebral weight and volume, which explains why the spongiform degeneration of the brain is ongoing with gradual enlargement of the head circumference.When the disease is more advanced, the initial oedematous swelling of the white matter will transform into brain atrophy with ventriculomegaly.

According to the demyelination/demyelination theory of CD, an acetate deficit causes myelin layers to be loosely bound and incomplete, which results in vacuoles in the interstitial space.

High NAA levels in the brain are also believed to be hazardous (oxidative stress theory), particularly when associated with concomitant ASPA deficiency as demonstrated in animal research. The intersection of grey and white matter (subcortical arcuate “U”-fibres) exhibits the severe effects of myelin degradation in imaging and histological investigations. The results of neuroimaging studies develop over time and demonstrate a centripetal spread to the core white matter. Unlike the white matter of the brain stem and cerebellum, the corpus callosum and internal capsules are unaffected; instead, the thalamus and globus pallidus are frequently affected (85)(86).Lack of motor development, eating issues, unusual muscle tone (weakness or stiffness), and an unusually huge, uncontrollably moving head are among symptoms. There's also a chance of losing your hearing or being paralysed. The usual behaviour of children is meekness and passivity. Macrocephaly, seizures, CNS vacuolation, and

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hypomyelination are all symptoms of Canavan disease, a rare neurometabolic disorder of the white matter that is linked to toxic accumulation of N-acetyl aspartate (NAA). N-acetyl aspartate synthesis generates NAA, which ASPA catabolizes in Canavan disease, missenses mutation renders ASPA ineffective, causing NAA to build up in the body. Clinical goals for gene therapy to correct the defective ASPA gene in patient with Canavan disease have not been met to yet (87).

When new-borns display the defining symptoms of the condition, Canavan illness may be suspected (e.g.- poor head control, macrocephaly, etc.) A comprehensive clinical assessment, a thorough patient history, and several specialist tests may be used to confirm a diagnosis. Gas chromatography mass spectrometry, a tool that may identify high amount of NAA in the urine, may be used in this examination. Additionally, elevated NAA concentrations have been found in the blood and cerebrospinal fluid (CSF). The absence of the enzyme aspartoacylase.

Can be detected by testing certain connective tissue cells (cultured fibroblasts) from the skin. Additionally lacking in white blood cells is aspartoacylase activity.

By measuring the concentration of NAA in the fluid around the growing foetus (amniotic fluid) between 16 to 18 weeks of gestation, amniocentesis can be used to diagnose Canavan illness in utero. Chorionic villus sampling (CVS), which involves removing a sample of placental cells at 10- 12 weeks gestation for mutation screening is a prenatal diagnosis option if both parents have known ASPA gene mutation (88)(89).

TREATMENT

Therapeutic approaches to CD

Treatment is typically supportive because there is currently no effective cure for the condition, which results in death at 2 to 5 years. (90). Nevertheless, genetic therapies are being tested and appear to lower the level of NAA in the brain. (91). There isn't a precise course of action. To lessen the effects of the condition, supportive treatment is crucial. Research is being done on lithium and gene therapy. (92).The focus of supportive care is on protecting the airway, treating infectious illnesses, and ensuring enough nourishment and hydration.

The family of those who are suffering from the disease can access hospice care (93). Children benefit from early intervention and special education programmes, other therapies to improve communication skills (particularly in those with a more gradual clinical course), and physical therapy to reduce contractures and maximise capacities and seated posture. (94). The use of anti-seizure medicine is an option for treating seizures.

When swallowing problems are present, a feeding gastrostomy may be necessary to maintain a sufficient intake of fluids.To reduce spasticity, Botox® injections may be utilised. By exercising and switching positions, contractures and decubiti can be avoided.Aspiration risk is increased by feeding issues and seizures;however, it can be decreased by using a G-tube (95). It Is advised that a paediatric neurologist perform follow-up exams every six months to assess the child's developmental condition and look for any signs of new issues (96).

In order to evaluate the treatments long term safety and effectiveness, a trial of AAV2 gene therapy was carried out in a few Canavan Disease patients. There were little side effects from utilising these medications, according to long term findings (at least five years after treatment). Furthermore, the patients NAA levels fell, which halted the course of brain cell death. Overall, the patient's clinical conditions did improve a little. Early administration of this therapy would be necessary for it to be most effective (possibly less than four months.) Thus, more study into early diagnosis is important.

Table 2 : The Different Types Of Therapies Used For Canavan Diseases

NAME OF THE THERAPY	RESULT
ACETALZOMIDE	Over the course of five months, lower the water concentration and NAA level in the white matter, Despite not lowering either of these, this drug decreased intracranial pressure.
KETOGENIC DIET	Increased beta hydroxybutyrate levels in the brain but had no effect on NAA levels
ACETATE SUPPLEMENT	Acetate supplementation can restore normal myelin formation and maintenance, which prevents the myelin breakdown seen in Canavan.

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	However, this does not address the building of NAA
LITHIUM	However, muscular tone and spastic dysplasia did not improve, brain and urine NAA levels fell, alertness and visual tracking both improved.
ENZYME REPLACEMENT THERAPY	Because molecular must be able to penetrate the blood brain barrier, enzyme replacement therapy is difficult in Canavan disease. Patients quality of life has not improved as a result of several interventions designed to aid with this.
STEM CELL THERAPY	Experts in the field stem cells are investigating the possible therapeutics use of stem cells in the case of Canavan sickness. Since stem cell therapy is still in its infancy, there aren't any urgent plans to use it for treatment or clinical trials.

(97)(98)(99)(100)

Clinical Outcome In Canavan Disease Patients After Gene Therapy

A validated measure of gross motor function in people with cerebral palsy and brain injury, the gross motor function measure is a typical tool for tracking changes in gross motor function over time in the general population (101). because Canavan disease is characterised by severe truncal hypotonia and instability, lack of head support, and limb spasticity, it is intended to measure how much of an activity a child can complete rather than the quality of their motor performance across five dimensions while lying down, sitting, crawling, standing and walking. By concentrating on the three functional categories with the lowest priority as the main objective areas. The child's capacity to roll from prone posture, as well as aspects of head control, which is severely compromised in Canavan illness, are characteristics considered in this examination.

After therapy, there was a small but statistically significant improvement in the lying subscale of the GMFM using the generalised linear mixed model technique as measured by the pre/post difference (102)(103).

Non-Genetic Therapeutic Approaches To CD

Most non-genetic CD therapy methods up to this point have concentrated on either reducing NAA buildup in the CNS or treating the metabolite imbalance brought on by poor NAA hydrolysis. Dysmyelination and osmotic-mediated diseases have both been linked to the pathological profile of CD.

1. Reduction of CNS NAA levels

Those who believe that NAA accumulation in the CNS through mechanisms like disrupted osmoregulation is the primary cause of CD pathogenesis have searched for drugs that could reverse the pathology associated with CD by reducing CNS NAA levels, as measured by high-performance liquid chromatography (HPLC) analysis. Although experiments have shown that ethanol (104)(105) sodium valproate (106)

additionally to pyrazole and some of its derivatives(104)When these compounds were examined in a CD animal model, no substantial decreases were seen, despite the fact that their capacity to lower NAA levels in animal brains without disease made them seem to be promising candidates.(107)The CD-like tremor rat, which has a CD-like condition due to a naturally occurring deletion of the ASPA gene, was the animal model employed in this instance to simulate CD.(108) According to O'Donnell et al., Li in the forms of Li citrate ($Li_3C_6H_5O_7$) and Li chloride (LiCl) are the only compounds that have consistently reduced CNS NAA levels in both animals and people, both with and without sickness.(106)have demonstrated that giving rats LiCl at a daily dose of 170 mg/kg of body weight for 2 weeks reduced brain NAA levels by 9%, while Baslow et al.(107)that evaluated it on CD-like tremor rat models and emphasised its potential therapeutic efficacy in CD. Following the daily treatment of LiCl at a dose of 300 mg/kg of body weight for four days, brain NAA levels in CD-like tremor rat CNS samples were shown to have decreased by 13%.(107) It's interesting to note that $Li_3C_6H_5O_7$ was later tested on a patient with CD.(109)however, NAA levels decreased in all studied CNS regions in both the

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white and the grey matter, as measured by proton magnetic resonance spectroscopy (MRS) studies. and only one of the four CNS regions studied achieved statistically significant reduction of NAA levels. The 18-month-old female CD patient was given Li3C6H5O7 up to 45 mg/kg of body weight per day for four months, and her magnetic resonance imaging (MRI) scans revealed that T1 weighted image changes in white matter were more similar to age-matched values for healthy human subjects (than they were theoretically for CD patients), indicating that myelination was more normal as a result of the Li-treatment.(109)Her clinical symptoms also looked to have slightly improved, as the patient had enhanced alertness, heightened awareness of her environment, and slight gains in verbal and gross motor skills.(109)Another human trial, this time involving six patients and lasting 60 days(110) grey matter (from MRI T1 relaxation times). Additionally, increased social interactions and attentiveness were noticed, but tests of gross motor ability revealed no statistically significant improvement.(110)In a more recent case report, Li3C6H5O7 was once more reported to lower CNS NAA levels when given to a 3-month-old female CD patient for a year at a dosage of 45 mg/kg per day. A 20% reduction in CNS NAA levels was attained, and the drug was once more well-tolerated. Additionally, although hypotonia and spasticity continued, attentiveness and visual tracking were observed to have improved.(111)Symptomatic benefits after Li treatment were moderate in every instance, but outcomes were reliable and there were no side effects observed for up to a year after intake. Studies on the safety of higher Li dosages in animals may be a useful requirement before making any clinical attempts because it is probable that higher dosages may be needed to observe better therapeutic efficacy. Unknown 4 is the mechanism by which Li reduces CNS NAA levels. It has been proposed that altering blood-brain barrier (BBB) permeability can inhibit NAA release from neurons or accelerate expulsion from the central nervous system (CNS)(109). Inhibition of the NAA synthesis pathways is a different method that might be targeted(112)This could either be done by inhibiting aspartate N-acetyltransferase (AspNAT; the enzyme that synthesises NAA from Asp and Acetyl-CoA) competitively or irreversibly, or it could be done by inhibiting NAAG-peptidase to stop NAA synthesis from NAAG hydrolysis; the latter is covered in more detail below.

2. Water removal

Baslow and Guilfoyle(115) have recently suggested that maintaining a sustained rise in plasma NAA levels in CD patients with oral NAA administration may be therapeutic in order to lessen oedema and other osmotic effects of the brain parenchyma found in the condition. They assert that because NAA is assumed to be unable to cross the blood-brain barrier, NAA buildup in plasma would increase plasma oncotic pressure and could lead to the establishment of an outward water gradient from the CNS ECF to the vasculature, allowing water to leave the brain(115).Studies to test this theory have not yet been done, though.

3. Accumulation of NAA and oxidative stress

Due to data that suggests CNS NAA buildup may cause harm by sparking oxidative stress (116)(117)(118) Antioxidants have been proposed as a possible CD therapy. When given before acute NAA administration (40 mg/kg of body weight, intraperitoneally, two days prior to NAA), all signs of oxidative stress induced by NAA were prevented. Lipoic acid, which is known to cross the BBB and to have a high potency, was tested for its ability to reduce signs of NAA-induced oxidative stress in 14-day-old Wistar rats. Rats pre-treated with lipoic acid did not experience any of the negative consequences that were observed in rats given NAA alone, including increased lipid peroxidation, protein oxidation, and DNA damage, as well as diminished enzymatic and nonenzymatic defences.(119)These findings imply that dietary supplementation with lipoic acid might be an effective strategy for treating CD, but more research must first demonstrate clinical relief in more suitable CD animal models.

4. Supplementation of Ac

Other research have sought to restore myelination by Ac-supplementation by concentrating on the "Ac-myelin-lipid" concept.(120-124)To this goal, the ability of glyceryl triacetate (GTA) and calcium acetate (CA) to transport ac to the CNS has been examined [67,68]. Even though both substances were proven to be generally safe, intragastric injection of similar doses of GTA or CA to 21-day-old C57BL/6 mice revealed that GTA significantly increased CNS Ac levels and did so with fewer side effects than CA(122)(123).

A few years later, GTA was demonstrated to be safe when given orally in high doses to tremor rat pups and modest doses to CD newborn patients,

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albeit it was ineffective in treating the CD-related symptomatology in the human experiment(114). A further investigation [65] on tremor rats revealed that high-dose injection of GTA resulted in enhanced CNS galactocerebroside 6levels, decreased spongy vacuolation, and better motor function. Furthermore, the medication was well-tolerated once more because no harmful side effects were reported(120).Given that GTA was successfully tolerated at high doses in rats, high-dose tests (4.5 g/kg of body weight per day) were conducted on 8-month-old CD infants and 1-year-old CD infants over the course of 4.5 and 6 months, respectively. During this time, neither toxicity nor motor improvements were noticed. The latter was linked to the treatment's delayed start(124) Additionally, it should be highlighted that GTA has demonstrated modest efficacy in humans at its greatest dosage to date, although treatment at a younger age may alleviate symptoms (as was the case in tremor rats), and should be taken into account when planning future research.

5. Energetic substrates

The anaplerotic triglyceride "triheptanoin" is another dietary supplement suggested for use as a non-genetic treatment approach to CD. By strengthening the connection between fatty acid production and oxidative energy metabolism, it is possible to expand on the finding that insufficient NAA hydrolysis results in acute oxidative stress(125).Francis et al. made an effort to restore oxidative integrity by offering substitute substrates for generating energy. In that study, 3-week-old nur7 pups and last week of pregnancy nur7 mice mutants were given chow that contained 35% triheptanoin (as caloric composition) until 12-weeks of age. Analysis of the animals' brains at 12 weeks revealed significantly decreased levels of oxidative stress, oligodendrocyte degeneration, and dysmyelination, whereas accelerated rotarod testing results at this time suggested enhanced motor function. Notably, mice that had previously received treatment displayed the biggest improvements in all specified criteria(126).Triheptanoin was chosen because it can both make TCA cycle intermediates and provide substrates for lipogenesis. Its exact mechanism of how it gives substrates to oligodendrocytes is still unknown, though.

6. Cell therapy

ASPA for the CNS is mostly produced by oligodendrocytes(127). maybe the most significant(128-130). Repopulating a CD patient's brain with functional oligodendrocytes may be able to reverse much of the disease's phenotype by restoring normal NAA metabolism. In the CD mouse model, neural stem cells have produced oligodendrocytes successfully(131). and although the clinical effects of such a treatment have not yet been examined, these oligodendrocytes exhibited a myelin-specific enzyme indicative of their capacity to produce myelin. Despite the fact that the juvenile treated mice's mice's neural progenitor cells (NPCs) survival rate was generally high(131).The limited migration of these cells indicates that there is still more work to be done before any effects (if found) are widespread enough to have an effect on the brain disease associated with this disorder. Along with the potential for migration, the stability(132).Moreover, the safety of differentiated and transplanted NPCs in the CNS of CD mice has not yet been established, and finding enough NPCs for human transplantation is probably going to be challenging(133). The NPCs employed in the aforementioned work were also evaluated for their potential to serve as ASPA gene therapy vectors. Juvenile CD mice were transplanted after 4 weeks, and enzyme activity testing revealed that ASPA activity was 16% of that observed in wild-type mice. But 5 weeks following the transplant, it was shown that this activity had decreased in adult mice, possibly as a result of the retroviral vector pLXIN's transient in vivo expression(131).It should be noted that using adeno-associated viral vectors has been hypothesised to improve treatment's long-term efficacy. If ASPA activity can be adequately elevated using this technique, more research should be done to determine whether CD animal models will exhibit any phenotypic improvements. Once again, it will be important to take into account the security, continuity, and movement of NPCs.

7. Novel pharmaceutical approaches

Topiramate, an anti-convulsant, was observed to reduce the rate of head growth in two CD patients after being administered for 7 and 15 months, starting at age 6 months for both kids. The exact mechanisms causing this impact are unknown, however Topçu et al(134).suggested that CNS water buildup was decreased, possibly through the suppression of carbonic anhydrase. Even though topiramate has very little benefit for CD patients, understanding the processes by which it works could offer more light on the pathology of the illness and support the aforementioned "osmotic-hydrostatic" concept.

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8. Blocking of NAAG catabolism

Baslow and Guilfoyle considered the possibility that the significant amounts of NAA that build up in CD patients' white matter could result from NAAG catabolism(112).have proposed that the process involves the use of NAAG-peptidase inhibitors or the metabotropic glutamate receptor 3 (GRM3 or mGluR3; the natural astrocytic surface target for NAAG). Adversaries and agonists(135) potentially impede the progression of dysmyelination

PHYSICAL EXAM

A neurologist graded the clinical results of the Canavan physical examination and compares them to the clinical examinations conducted at earlier visits prior to gene transfer. As part of the quality-of-life assessment, the exam also includes caregivers' narrative remarks. Result was broken down into levels of alertness, head lag, optic atrophy, cranial nerve exam, capacity to fixate on objects, visual tracking, truncal and extremity tone, spontaneous movement of extremities and fine motor function, sensory exam, and reflexes (136).

II. CONCLUSION

The ASPA gene can develop mutations that lead to Canavan disease, a hereditary neurological disorder. Development delay, head lag, hypotonia, and macrocephaly are significant clinical indicators. The level of NAA in the patient's urine are high. There is growing evidence that there is a considerable variety in the clinical phenotype of Canavan illness, even though it is frequently assumed that kids with the condition will pass away in childhood. Even though it affects people of all races equally, there is relatively little known about its prevalence in groups of Jews who are not of Ashkenazi heritage. To lay the groundwork for fresh therapy modalities, ongoing research attempts to better understand Canavan illness and underlying causes.

REFERANCE

[1]. Canavan MM. Schilders encephalitis diffusa. Arch Neural Psychiat 1931; 25: 299-308

[2]. Farouk T. First Record Mutations in the Genes ASPA and ARSA Causing Leukodystrophy in Jordan. Biomed Res Int. 2019;7235914https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6374869/

[3]. Pleasure D, Guo F, Chechenia O, Bannerman P, McDonough J, Burns T, Wang Y, Hull V. Pathophysiology and Treatment of Canavan Disease. Neurochem Res. 2020;45(3):561-565.https://link.springer.com/article/10.1007/s11064-018-2693-6

[4]. Dembic M, Andersen HS, Bastian J, Doktor TK, Corydon TJ, Sass JO, Lopes Costa A, Douai F, Andresen BS. Next generation sequencing of RNA reveals novel targets of resveratrol with possible implications for Canavan disease. Mol Genet Metab. 2019 Jan;126(1):64-76 https://pubmed.ncbi.nlm.nih.gov/30446350/

[5]. Starling S. White matter disease: Targeted aspartoacylase gene therapy reverts Canavan disease. Nat Rev Neurol. 2018 Jan;14(1):4.

[6]. Adorate BT, O'Brien JS, Lampert PW, Roe TF, Neu stein HB. Cerebral spongy degeneration of infancy: A biochemical and ultrastructural study of affected twins. Neurology. 1972;22(2):202–10https://pubmed.ncbi.nlm.nih.gov/4333033/

[7]. Banker BQ, Robertson JT, Victor M. Spongy Degeneration of the Central Nervous System in Infancy. Neurology. 1964; 14:981–1001.

[8]. Chou SM, Weisman HA. Spongy Degeneration of the Central Nervous System: Case of Homocystinuria. Arch Pathol. 1965; 79:357–63https://pubmed.ncbi.nlm.nih.gov/14254905/

[9]. Feigenbaum A, Moore R, Clarke J, Hewson S, Chitayat D, Ray PN, et al. Canavan disease: carrier-frequency determination in the Ashkenazi Jewish population and development of a novel molecular diagnostic assay. Am J Med Genet A. 2004;124a (2):142–7.https://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.20334

[10]. Feigenbaum A, Moore R, Clarke J, Hewson S, Chitayat D, Ray PN, et al. Canavan disease: Carrier-frequency determination in the Ashkenazi Jewish population and development of a novel molecular diagnostic assay. Am J Med Genet A 2004;124A: 142-7.https://pubmed.ncbi.nlm.nih.gov/146996

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12/#:~:text=Canavan%20disease%20(CD)%20is%20an,%3A37%2D1%3A40.

[11]. Hoshino H1, Kubota M. Canavan disease: clinical features and recent advances in research. Podiatry Int Aug 2014; 56:477-83.https://onlinelibrary.wiley.com/doi/10.1111 /ped.12422

[12]. Karim Zadeh P, Jafari N, Bulgari HN, Rahimi an E, Ahmadabadi F, Nemati H, et al. The clinical features and diagnosis of Canavan's disease: A case series of Iranian patients. Iran J Child Neurol 2014; 8:66-71.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4307371/

[13]. Ashrafi MR, Tavasoli AR, Katibeh P, Aryani O, Vafaee-Shahi M. A novel mutation in aspartoacylase gene; Canavan disease. Iran J Child Neurol 2015; 9:54-7.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4670978/

[14]. Beaudet AL. Aspartoacylase Deficiency (Canavan Disease). In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic and Molecular Basis of Inherited Disease, 8th ed. McGraw-hill, New York, 2001, 5799-5805

[15]. Olsen TR, Tranebjaerg L, Kvittingen EA, et al., Two novel aspartoacylase gene (ASPA) missense mutation specific to Norwegian and Swedish patients with Canavan disease. J Med Genet. 2002; 39:55-8

[16]. Surendra S, Michal's- Matalon K, Quast MJ, et al. Canavan disease: a monogenic trait with complex genomic interaction. Mol Genet Metab. 2003; 80:74-80

[17]. VonJonquiere's G, Spencer ZHT, Rowlands BD, Klugman CB, Bogner's A, Harasta AE, Parley KE, et al. Uncoupling N-acetyl aspartate from brain pathology: implications for Canavan disease gene therapy. Acta Neuropathology. 2018 Jan;135(1):95-113.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5756261/

[18]. Moffett JR, Ross B, Arun P, Madhava Rao CN, Namboodiri AM. N-Acetyl aspartate in the CNS: from neurodiagnostic to neurobiology. Prog Neurobiology. 2007; 81:89–131.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1919520/

[19]. Rae CD. A guide to the metabolic pathways and function of metabolites observed in human brain 1H magnetic resonance spectra. Neurochem Res. 2014; 39:1–36.https://link.springer.com/article/10.1007/s11064-013-1199-5

[20]. Martin E, Capone A, Schneider J, Hennig J, Theil T. Absence of N-acetyl aspartate in the human brain: impact on neurospectroscopy Ann Neurol. 2001; 49:518–521.https://pubmed.ncbi.nlm.nih.gov/11310630/

[21]. Kaul R, Gao GP, Balamurugan K, Matalon R. Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. Nat Genet. 1993; 5:118–123.https://www.nature.com/articles/ng1093-118

[22]. Madhava Rao CN, Arun P, Moffett JR, Szucs S, Surendra S, Matalon R, Garbern J, Hristov D, Johnson A, Jiang W, et al. Defective N-acetyl aspartate catabolism reduces brain acetate levels and myelin lipid synthesis in Canavan's disease. Proc Natl Accad Sci USA. 2005; 102:5221–5226.https://www.pnas.org/doi/full/10.1073/pnas.0409184102

[23]. Leone P, Shera D, McPhee SW, Francis JS, Kolodny EH, Bilaniuk LT, Wang DJ, Assadi M, Goldfarb O, Goldman HW, et al. Long-term follow-up after gene therapy for Canavan disease. Sci Trans Med. 2012; 4:165https://www. science.org/ doi/10.1126 /scitranslmed. 3003454

[24]. Rigdon GC. Differential effects of apomorphine on repulse inhibition of acoustic startle reflex in two rat strains. Psychopharmacology. 1990; 102:419–421.https://link.springer.com/article/10.1007/BF02244115#article-info

[25]. Francis JS, Wojtas I, Markov V, Gray SJ, McCown TJ, Samulski RJ, Bilaniuk LT, Wang DJ, De Vivo DC, Janson CG, et al. N-acetyl aspartate supports the energetic demands of developmental myelination via oligodendroglial aspartoacylase.2016;96:323-334 https://www.sciencedirect.com/science/article/abs/pii/S0969996116302340?via%3Dihub

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 802-820 www.ijprajournal.com ISSN: 2249-7781

[26]. Ahmed SS, Li H, Cao C, Sikoglu EM, Denninger AR, Su Q, Eaton S, Liso Navarro AA, Xie J, Szucs S, et al. A single intravenous rAAV injection as late as P20 achieves efficacious and sustained CNS gene therapy in Canavan mice. Mol Ther. 2013; 21:2136–2147.https://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC3863789&blobtype=pdf

[27]. Gessler DJ, Li D, Xu H, Su Q, Sanmiguel J, Tuncer S, Moore C, King J, Matalon R, Gao G.Redirecting N-acetylaspartate metabolism in the central nervous system normalizes myelination and rescues Canavan disease. JCI Insight. 2017;2 https://insight.jci.org/articles/view/90807

[28]. Cahoy JD, Emery B, Kaushal A, Foo LC, Zamanian JL, Christopherson KS, Xing Y, Lubischer JL, Krieg PA, Krupenko SA, et al. A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. J Neurosci. 2008; 28:264–278.

[29]. Madhavarao CN, Moffett JR, Moore RA, Viola RE, Namboodiri MA, Jacobowitz DM. Immunohistochemical localization of aspartoacylase in the rat central nervous system. J Comp Neurol. 2004; 472:318–329.

[30]. Mersmann N, Tkachev D, Jelinek R, Roth PT, Mobius W, Ruhwedel T, Ruhle S, Weber-Fahr W, Sartorius A, Klugmann M. Aspartoacylase-LacZ Knockin Mice: an engineered model of Canavan disease. PLoS ONE. 2011;6

[31]. Ahmed SS, Schattgen SA, Frakes AE, Sikoglu EM, Su Q, Li J, Hampton TG, Denninger AR, Kirschner DA, Kaspar B, et al. raav gene therapy in a Canavan's disease mouse model reveals immune impairments and an extended pathology beyond the central nervous system. Mol Ther. 2016; 24:1030–1041.

[32]. Ahmed SS, Li H, Cao C, Sikoglu EM, Denninger AR, Su Q, Eaton S, Liso Navarro AA, Xie J, Szucs S, et al. A single intravenous rAAV injection as late as P20 achieves efficacious and sustained CNS gene therapy in Canavan mice. Mol Ther. 2013; 21:2136–2147.

[33]. Guo F, Bannerman P, Mills Ko E, Miers L, Xu J, Burns T, Li S, Freeman E, McDonough JA, Pleasure D. Ablating N-acetylaspartate prevents leukodystrophy in a Canavan disease model. Ann Neurol. 2015; 77:884–888.

[34]. Mosser, J. et al. Nature 361,726-730 (1993)

[35]. Kaul, R., Gao, G. P., Balamurugan, K & Matalon, R. nature Genet. 5, 118-123(1993)

[36]. Maier H, Wang-Eckhardt L, Hartmann D, Gieselmann V, Eckhardt M. N-Acetylaspartate synthase deficiency corrects the myelin phenotype in a Canavan disease mouse model but does not affect survival time. J Neurosci. 2015; 35:14501–14516.

[37]. Sohn J, Bannerman P, Guo F, Burns T, Miers L, Croteau C, Singhal NK, McDonough JA, Pleasure D. Suppressing N-acetyl-l-aspartate synthesis prevents loss of neurons in a murine model of Canavan leukodystrophy. J Neurosci. 2017; 37:413–421.

[38]. Matalon, R, Michals -Matalon K. Gene Reviews website. Updated August 11,2011. Retrieved April 29, 2016, from http://www.ncbi.nlm.nih.gov/books/NBK1234/

[39]. Meri R. Bokhari, Debopam Samantau, Syed Rizwan A. Bokhari. Article on Canavan disease. Stat pearls publication LLC;2022 http://www.ncbi.nlm.nih.gov/books/NBK430816/

[40]. Baslow MH, Hrabe J, Guilfoyle DN. Dynamic relationship between neurostimulation and N-acetylaspartate metabolism in the human visual cortex: Evidence that NAA functions as a molecular water pump during visual stimulation. J. Mol. Neurosci. 2007; 32: 235– 245.

[41]. Wolf NI, Willemsen MA, Engelke UF et al. Severe hypomyelination associated with increased levels of N-acetylaspartylglutamate in CSF. Neurology 2004; 62: 1503– 1508.

[42]. Kolodziejczyk K, Hamilton NB, Wade A, Karadottir R, Attwell D. The effect of N-acetyl-aspartyl-glutamate and N-acetyl-aspartate on white matter oligodendrocytes. Brain 2009; 132: 1496–1508.

[43]. Baslow MH. Brain N-acetylaspartate as a molecular water pump and its role in the etiology of Canavan disease: A mechanistic explanation. J. Mol. Neurosci. 2003; 21: 185–190
[44]. Tranberg M, Stridh MH, Guy Y et al. NMDA-receptor mediated efflux of N-acetylaspartate: Physiological and/or pathological importance? Neurochem. Int. 2004; 45: 1195–1204.
[45]. Klugmann M, Leichtlein CB, Symes CW, Serikawa T, Young D, During MJ. Restoration of aspartoacylase activity in CNS neurons does not ameliorate motor deficits and demyelination in a model of Canavan disease. Mol. Ther. 2005; 11: 745–753.
[46]. Clarner T, Wieczorek N, Krauspe B, Jansen K, Beyer C, Kipp M. Astroglial redistribution of aquaporin 4 during spongy degeneration in a Canavan disease mouse model. J. Mol. Neurosci. 2014; 53: 22–30.
[47]. Hagenfeldt L, Bollgren I, Venizelos N. N-acetylaspartic aciduria due to aspartoacylase deficiency: A new aetiology of childhood leukodystrophy. J. Inherit. Metab. Dis. 1987; 10: 135–141.
[48]. Bluml S. In vivo quantitation of cerebral metabolite concentrations using natural abundance 13C MRS at 1.5 T. J. Magn. Reson. 1999; 136: 219–225
[49]. Kumar S, Mattan NS, de Vellis J. Canavan disease: A white matter disorder. Ment. Retard. Dev. Disabil. Res. Rev. 2006; 12: 157–165.
[50]. Madhavarao CN, Arun P, Moffett JR et al. Defective N-acetylaspartate catabolism reduces brain acetate levels and myelin lipid synthesis in Canavan's disease. Proc. Natl Acad. Sci. U.S.A. 2005; 102: 5221–5226.
[51]. Wang J, Leone P, Wu G et al. Myelin lipid abnormalities in the aspartoacylase-deficient tremor rat. Neurochem. Res. 2009; 34: 138–148.
[52]. Francis JS, Strande L, Markov V, Leone P. Aspartoacylase supports oxidative energy metabolism during myelination. J. Cereb. Blood Flow Metab. 2012; 32: 1725–1736.
[53]. Moffett JR, Namboodiri MA, Cangro CB, Neale JH. Immunohistochemical localization of N-acetylaspartate in rat brain. Neuroreport 1991; 2: 131–134.
[54]. Bhakoo KK, Pearce D. In vitro expression of N-acetyl aspartate by oligodendrocytes: Implications for proton magnetic resonance spectroscopy signal in vivo. J. Neurochem. 2000; 74: 254–262.
[55]. Baslow MH, Suckow RF, Sapirstein V, Hungund BL. Expression of aspartoacylase activity in cultured rat macroglial cells is limited to oligodendrocytes. J. Mol. Neurosci. 1999; 13: 47–53.
[56]. Bhakoo KK, Craig TJ, Styles P. Developmental and regional distribution of aspartoacylase in rat brain tissue. J. Neurochem. 2001; 79: 211–220.
[57]. Chakraborty G, Mekala P, Yahya D, Wu G, Ledeen RW. Intraneuronal N-acetylaspartate supplies acetyl groups for myelin lipid synthesis: Evidence for myelin-associated aspartoacylase. J. Neurochem. 2001; 78: 736–745.
[58]. Mattan NS, Ghiani CA, Lloyd M et al. Aspartoacylase deficiency affects early postnatal development of oligodendrocytes and myelination. Neurobiol. Dis. 2010; 40: 432–443.
[59]. (59)Kumar S, Biancotti JC, Matalon R, de Vellis J. Lack of aspartoacylase activity disrupts survival and differentiation of neural progenitors and oligodendrocytes in a mouse model of Canavan disease. J. Neurosci. Res. 2009; 87: 3415–3427.
[60]. Baslow MH, Guilfoyle DN (2013) Canavan disease, a rare early-onset human spongiform leukodystrophy: insights into its genesis and possible clinical interventions. Biochimie 95:946-956
[61]. D'Adamo AF Jr, Yatsu FM (1966) Acetate metabolism in the nervous system. NAcetyl-L-aspartic acid and the biosynthesis of brain lipids. J Neurochem 13:961-965
[62]. Janson CG, Kolodny EH, Zeng BJ, Raghavan S, Pastores G, Torres P, Assadi M, McPhee S, Goldfarb O, Saslow B, Freese A, Wang DJ, Bilaniuk L, Shera D, Leone P (2006) Mild-onset presentation of Canavan's disease associated with novel G212A point mutation in aspartoacylase gene. Ann Neurol 59:428-431
[63]. Velinov M, Zellers N, Styles J, Wisniewski K (2008) Homozygosity for

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 2 Mar-Apr 2023, pp: 802-820 www.ijprajournal.com ISSN: 2249-7781

mutation G212A of the gene for aspartoacylase is associated with atypical form of Canavan's disease. Clin Genet 73:288-289

[64]. Madhavarao CN, Moffett JR, Moore RA, Viola RE, Namboodiri MA, Jacobowitz DM (2004) Immunohistochemical localization of aspartoacylase in the rat central nervous system. J Comp Neurol 472:318-329

[65]. Kirmani BF, Jacobowitz DM, Namboodiri MA (2003) Developmental increase of aspartoacylase in oligodendrocytes parallels CNS myelination. Brain Res Dev Brain Res 140:105-115

[66]. Baslow MH, Suckow RF, Sapirstein V, Hungund BL (1999) Expression of aspartoacylase activity in cultured rat macroglial cells is limited to oligodendrocytes. J Mol Neurosci 13:47-53

[67]. Baslow MH (2003) Brain N-acetylaspartate as a molecular water pump and its role in the etiology of Canavan disease: a mechanistic explanation. J Mol Neurosci 21:185190

[68]. Sager TN, Fink-Jensen A, Hansen AJ (1997) Transient elevation of interstitial Nacetylaspartate in reversible global brain ischemia. J Neurochem 68:675-682

[69]. Wang J, Matalon R, Bhatia G, Wu G, Li H, Liu T, Lu ZH, Ledeen RW (2007) Bimodal occurrence of aspartoacylase in myelin and cytosol of brain. J Neurochem 101:448-457

[70]. Vajda Z, Berényi E, Bogner P, Repa I, Dóczi T, Sulyok E (1999) Brain adaptation to water loading in rabbits as assessed by NMR relaxometry. Pediatr Res 46:450-454

[71]. Redzic Z (2011) Molecular biology of the blood-brain and the blood-cerebrospinal fluid barriers: similarities and differences. Fluids Barriers CNS 8:3

[72]. Francis JS, Strande L, Markov V, Leone P (2012) Aspartoacylase supports oxidative energy metabolism during myelination. J Cereb Blood Flow Metab 32:1725-1736

[73]. Francis JS, Markov V, Leone P (2014) Dietary triheptanoin rescues oligodendrocyte loss, dysmyelination and motor function in the nur7 mouse model of Canavan disease. J Inherit Metab Dis 37:369-381

[74]. Moffett JR, Ross B, Arun P, Madhavrao CN, Namboodiri MAA. N acetyl aspartate in the CNS: from neurodiagnostic to neurobiology. Prog Neurobiology 2007; 81:89-131

[75]. Der Knaap MS, Valk J. Canavan disease. In: Van der Knaap MS editor. Magnetic resonance of myelination and myelin Disorder. Berlin Heidelberg New Work: springer; 2005.pp326-333

[76]. Trott AA, Matalon KM, Matalon RK. Aspartic acid (Canavan disease). In: Kleigman, ed. Nelson Textbook of pediatrics.19th ed. Philadelphia: Saunders; 2011.pp455-6

[77]. Matalon R, Delgado L, Michals-Matalon K. Canavan Disease. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. University of Washington, Seattle; Seattle (WA): Sep 16, 1999

[78]. Merrill ST, Nelson GR, Longo N, Bonkowsky JL. Cytotoxic edema and diffusion restriction as an early pathoradiologic marker in canavan disease: case report and review of the literature. Orphanet J Rare Dis. 2016 Dec 07;11(1):169.

[79]. Gessler DJ, Gao G. Gene Therapy for the Treatment of Neurological Disorders: Metabolic Disorders.

[80]. AJ, Raybaud C (2018) Metabolic disorders that affect both gray and white matter. In: James BA (ed) Pediatric neuroimaging, 6th edn. Lippincott Williams & Wilkins, p 170

[81]. Taylor DLDS et al (1995) Investigation into the role of N-acetylaspartate in cerebral osmoregulation. J Neurochim 65(1):275–281.

[82]. Baslow MH (1999) Molecular water pumps and the aetiology of Canavan disease: a case of sorcerer's apprentice. J Inherit Metab Dis 22:99–101.

[83]. Ahmed SS, Gao G (2014) Making the white matter matters: progress in understanding Canavan's disease and therapeutic interventions through eight decades.

[84]. von Jonquiere's, G. et al. Uncoupling N-acetyl aspartate from brain pathology: implication for Canavan disease gene

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therapy. Acta Neuropathol 135, 95-113 (2018)

[85]. Appu AP, Moffett JR, Arun P et al (2017) Increasing N-acetylaspartate in the brain during postnatal myelination does not cause the CNS pathologies of Canavan disease. Front Mol Neurosci 10:161.

[86]. Gordon N. Canavan disease : a review of recent development Eur J Paediatr Neurol. 2001;5:65-69

[87]. Matalon R, Matalon KM. Canavan disease prenatal diagnosis and genetic counselling. Obstet Gynecol clin North Am. 2002:29:297-304

[88]. Bührer C, Bassir C, von Moers A, Sperner J, Michael T, Scheffner D, Kaufmann HJ (1993) Cranial ultrasound findings in aspartoacylase deficiency (Canavan disease). Pediatr Radiol 23:395–397.

[89]. Breitbach-Faller N, Schrader K, Rating D, Wunsch R (2003) Ultrasound findings in follow-up Investigations in a case of Aspartoacylase deficiency (Canavan disease). Neuropediatrics 34:96–99.

[90]. Gordon N. Canavan disease: a review of recent developments. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 5 (2): 65-9

[91]. Reddy N, Calloni SF, Vernon HJ, Boltshauser E, Huisman TAGM, Soares BP. Neuroimaging Findings of Organic Acidemias and Aminoacidopathies. (2018) Radiographics. 38 (3): 912-931.

[92]. Vanderver A, Wolf NI. Genetic and metabolic disorders of the white matter. In: Swaiman KF, Ashwal S, Ferriero DM, et al, eds. Swaiman's Pediatric Neurology: Principles and Practice. 6th ed. Philadelphia, PA: Elsevier; 2017:chap 99.

[93]. Caliebe A, Vater I, Plendl H, Gesk S, Siebert R, Cremer FW, Klein-Hitpass L. A. 439 kb-sized homozygous deletion in 17p13.3 leading to biallelic loss of the ASPA as cause of Canavan disease detected by SNP-array analysis. Mol Genet Metab. 2010;99:184–5

[94]. Cozzolino M, Augello B, Carella M, Palumbo O, Tavazzi B, Amorini AM, Lazzarino G, Merla G, Brunetti-Pierri N. Chromosomal 17p13.3 microdeletion unmasking recessive Canavan disease mutation. Mol Genet Metab. 2011;104:706–7.

[95]. Delaney KE, Kralik SF, Hainline BE, Golomb MR. An atypical case of Canavan disease with stroke-like presentation. Pediatr Neurol. 2015;52:218–21.

[96]. Fares F, Badarneh K, Abosaleh M, Harari-Shaham A, Diukman R, David M. Carrier frequency of autosomal-recessive disorders in the Ashkenazi Jewish population

[97]. E.Bitto, C.A. Bingman, G.E. Wesenberg, J.G. McCoy, G. N. Phillips Jr., Structure of aspartoacylase, the brain enzyme impaired in Canavan disease. Proc. Natl. Acad. Sci.U.S.A. 104, 456-461 (2007)

[98]. G. Chakraborty, P. Mekala, D. Yahya, G. Wu, R.W. Ledeen, Intraneuronal N-acetyl aspartates supplies acetyl groups for myelin lipid synthesis: Evidence for myelin-associated aspartoacylase. J. Neurochem.78, 736-745 (2001)

[99]. C.N. Madhavarao, J,R, Moffett, R.A. Moore, R.E. Viola, M.A. Namboodiri, D.M. Jacobowitz, Immunological localization of aspartoacylase in the rat central nervous system.J. Comp. Neurol. 472, 318-329 (2004)

[100]. H.D. Yan, K. Ishihara, T. Serikawa, M. Sasa, Activation by N-acetyl-L-aspartate of acutely dissociated hippocampal neurons in rats via metabotropic glutamate receptors. Epilepsia 44, 1153-1159.(2003)

[101]. D. Russell, The Gross Motor Function Measure Manual (CanChild Centre for Childhood Disability Research, McMaster University, Hamilton, Canada, 1993)

[102]. S. W. McPhee, J. Francis, C. G. Janson, T. Seri Kawa, K. Hyland, E. O. Ong, S. S. Raghavan, A. Freese, P. Leone, Effects of AAV-2-mediated aspartoacylase gene transfer in the tremor rat model of Canavan disease. Brain Res. Mol. Brain Res. 135, 112–121 (2005).

[103]. R. Matalon, S. Surendran, P. L. Rady, M. J. Quast, G. A. Campbell, K. M. Matalon, S. K. Tyring,J. Wei, C. S. Peden, E. L. Ezell, N. Muzyczka, R. J. Mandel, Adeno-associated virus-mediated aspartoacylase gene transfer to the brain of knockout mouse for Canavan disease. Mol. Ther.7, 580–587 (2003).

[104]. Baslow MH, Suckow RF, Hungund BL (2000) Effects of ethanol and of alcohol dehydrogenase inhibitors on the reduction of N-acetylaspartate levels of brain in

mice in vivo: a search for substances that may have therapeutic value in the treatment of Canavan disease. J Inherit Metab Dis 23:684-692

[105]. Hirakawa K, Uekusa K, Sato S, Nihira M (1994) MRI and MRS studies on acute effects of ethanol in the rat brain. Nihon Hoigaku Zasshi 48:63-74

[106]. O'Donnell T, Rotzinger S, Nakashima TT, Hanstock CC, Ulrich M, Silverstone PH (2000) Chronic lithium and sodium valproate both decrease the concentration of myoinositol and increase the concentration of inositol monophosphates in rat brain. Brain Res 880:84-91

[107]. Baslow MH, Kitada K, Suckow RF, Hungund BL, Serikawa T (2002) The effects of lithium chloride and other substances on levels of brain N-acetyl-L-aspartic acid in Canavan disease-like rats. Neurochem Res 27:403-406

[108]. Kitada K, Akimitsu T, Shigematsu Y, Kondo A, Maihara T, Yokoi N, Kuramoto T, Sasa M, Serikawa T (2000) Accumulation of N-acetyl-L-aspartate in the brain of the tremor rat, a mutant exhibiting absence-like seizure and spongiform degeneration in the central nervous system. J Neurochem 74:2512-2519

[109]. Janson CG, Assadi M, Francis J, Bilaniuk L, Shera D, Leone P (2005) Lithium citrate for Canavan disease. Pediatr Neurol 33:235-243

[110]. Assadi M, Janson C, Wang DJ, Goldfarb O, Suri N, Bilaniuk L, Leone P (2010) Lithium citrate reduces excessive intra-cerebral N-acetyl aspartate in Canavan disease. Eur J Paediatr Neurol 14:354-359

[111]. Solsona MD, Fernández LL, Boquet EM, Andrés JL (2012) Lithium citrate as treatment of Canavan disease. Clin Neuropharmacol 35:150-151

[112]. Baslow MH, Guilfoyle DN (2009) Are astrocytes the missing link between lack of brain aspartoacylase activity and the spongiform leukodystrophy in Canavan disease? Neurochem Res 34:1523-1534

[113]. Makoukji J, Belle M, Meffre D, Stassart R, Grenier J, Shackleford G, Fledrich R, Fonte C, Branchu J, Goulard M, de Waele C, Charbonnier F, Sereda MW, Baulieu EE, Schumacher M, Bernard S, Massaad C (2012) Lithium enhances remyelination of peripheral nerves. Proc Natl Acad Sci U S A 109:3973-3978

[114]. Benedetti F, Bollettini I, Barberi I, Radaelli D, Poletti S, Locatelli C, Pirovano A, Lorenzi C, Falini A, Colombo C, Smeraldi E (2013) Lithium and GSK3-β promoter gene variants influence white matter microstructure in bipolar disorder. Neuropsychopharmacology 38:313-327

[115]. Baslow MH, Guilfoyle DN (2013) Canavan disease, a rare early-onset human spongiform leukodystrophy: insights into its genesis and possible clinical interventions. Biochimie 95:946-956

[116]. Pederzolli CD, Mescka CP, Scapin F, Rockenbach FJ, Sgaravatti AM, Sgarbi MB, Wyse AT, Wannmacher CM, Wajner M, Dutra-Filho CS (2007) N-Acetylaspartic acid promotes oxidative stress in cerebral cortex of rats. Int J Dev Neurosci 25:317-324

[117]. Pederzolli CD, Rockenbach FJ, Zanin FR, Henn NT, Romagna EC, Sgaravatti AM, Wyse AT, Wannmacher CM, Wajner M, de Mattos Dutra A, Dutra-Filho CS (2009) Intracerebroventricular administration of N-acetylaspartic acid impairs antioxidant defenses and promotes protein oxidation in cerebral cortex of rats. Metab Brain Dis 24:283-298

[118]. Surendran S, Bhatnagar M (2011) Upregulation of N-acetylaspartic acid induces oxidative stress to contribute in disease pathophysiology. Int J Neurosci 121:305-309

[119]. Pederzolli CD, Rosa AP, de Oliveira AS, Coelho JG, Becker Dda L, Dalazen GR, Moraes TB, Dutra-Filho CS (2010) Neuroprotective role of lipoic acid against acute toxicity of N-acetylaspartic acid. Mol Cell Biochem 344:231-239

[120]. Arun P, Madhavarao CN, Moffett JR, Hamilton K, Grunberg NE, Ariyannur PS, Gahl WA, Anikster Y, Mog S, Hallows WC, Denu JM, Namboodiri AM (2010) Metabolic acetate therapy improves phenotype in the tremor rat model of Canavan disease. J Inherit Metab Dis 33:195-210

[121]. Madhavarao CN, Arun P, Anikster Y, Mog SR, Staretz-Chacham O, Moffett JR, Grunberg NE, Gahl WA, Namboodiri AM (2009) Glyceryl triacetate for Canavan disease: a low-dose trial in infants and

evaluation of a higher dose for toxicity in the tremor rat model. J Inherit Metab Dis 32:640-650

[122]. Mathew R, Arun P, Madhavarao CN, Moffett JR, Namboodiri MA (2005) Progress toward acetate supplementation therapy for Canavan disease: glyceryl triacetate administration increases acetate, but not N-acetylaspartate, levels in brain. J Pharmacol Exp Ther 315:297-303

[123]. Namboodiri AM, Peethambaran A, Mathew R, Sambhu PA, Hershfield J, Moffett JR, Madhavarao CN (2006) Canavan disease and the role of N-acetylaspartate in myelin synthesis. Mol Cell Endocrinol 252:216-223

[124]. Segel R, Anikster Y, Zevin S, Steinberg A, Gahl WA, Fisher D, Staretz-Chacham O, Zimran A, Altarescu G (2011) A safety trial of high dose glyceryl triacetate for Canavan disease. Mol Genet Metab 103:203-206

[125]. Francis JS, Strande L, Markov V, Leone P (2012) Aspartoacylase supports oxidative energy metabolism during myelination. J Cereb Blood Flow Metab 32:1725-1736

[126]. Francis JS, Strande L, Markov V, Leone P (2012) Aspartoacylase supports oxidative energy metabolism during myelination. J Cereb Blood Flow Metab 32:1725-1736

[127]. Bhakoo KK, Craig TJ, Styles P (2001) Developmental and regional distribution of aspartoacylase in rat brain tissue. J Neurochem 79:211-220

[128]. Kirmani BF, Jacobowitz DM, Kallarakal AT, Namboodiri MA (2002) Aspartoacylase is restricted primarily to myelin synthesizing cells in the CNS: therapeutic implications for Canavan disease. Brain Res Mol Brain Res 107:176-182

[129]. Klugmann M, Symes CW, Klaussner BK, Leichtlein CB, Serikawa T, Young D, During MJ (2003) Identification and distribution of aspartoacylase in the postnatal rat brain. Neuroreport 14:1837-1840

[130]. Madhavarao CN, Hammer JA, Quarles RH, Namboodiri MA (2002) A radiometric assay for aspartoacylase activity in cultured oligodendrocytes. Anal Biochem 308:314319

[131]. Surendran S, Shihabuddin LS, Clarke J, Taksir TV, Stewart GR, Parsons G, Yang W, Tyring SK, Michals-Matalon K, Matalon R (2004) Mouse neural progenitor cells differentiate into oligodendrocytes in the brain of a knockout mouse model of Canavan disease. Brain Res Dev Brain Res 153:19-27

[132]. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, Paz N, Koren-Michowitz M, Waldman D, Leider-Trejo L, Toren A, Constantini S, Rechavi G (2009) Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 6:e1000029

[133]. Miranda CO, Brites P, Mendes Sousa M, Teixeira CA (2013) Advances and pitfalls of cell therapy in metabolic leukodystrophies. Cell Transplant 22:189-204

[134]. Topçu M, Yalnizoğlu D, Saatçi I, Haliloğlu G, Topaloğlu H, Senbil N, Onol S, Coşkun T (2004) Effect of topiramate on enlargement of head in Canavan disease: a new option for treatment of megalencephaly. Turk J Pediatr 46:67-71

[135]. Baslow MH (2008) The astrocyte surface NAAG receptor and NAAG peptidase signalling complex as a therapeutic target. Drug News Perspect 21:251-257

[136]. S. W. McPhee, C. G. Janson, C. Li, R. J. Samulski, A. S. Camp, J. Francis, D. Shera, L. Lioutermann, M. Feely, A. Freese, P. Leone, Immune responses to AAV in a phase I study for Canavan disease.J. Gene Med. 8, 577–588 (2006)