Newest therapeutic options for adrenoleukodystrophy

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ABSTRACT

X-linked adrenoleukodystrophy is a genetic disease correlated with mutation of ATP-binding cassette, which results in errors of peroxisomal beta oxidation and accumulation of impaired very long chain fatty acids. This leads to degeneration of adrenal glands, spinal cord and myelin sheaths. Despite nearly 100 years of ALD history, the treatment is limited to few therapeutic options, mainly Lorenzo’s Oil and Hematopoetic stem cell transplant. Available therapy can only slow the progression of the disease in early stages. The aim of our study was to present the newest therapeutic options in X-ALD. Substantial articles on new treatment of X-ALD from period 2007-2018 in the Asian, European and American regions have been analyzed. Among 219 articles in PubMed Medline database related to therapy and treatment of X-ALD, 13 articles were selected for analysis, reviewed and divided into two main groups: cause-related treatment (11 articles) and symptoms-related treatment (2 articles). Within cause-related treatment, the usage of known medications such as eg. pioglitazone, natural phenols - resveratrol, gene therapy with adenoassociated virus serotype 9 or combined therapies (Hematopoetic Stem Cell Gene Therapy) have been reviewed. Symptoms related treatment attempted to reduce spasticity and secondary dystonia in X-ALD patients. Reviewed research presents progress in development of treatment options for X-ALD, however still in primary in vitro and animal tested.
stages. Secondary neurological symptoms medication is awaiting for better solutions for ALD patients, in order to improve their Quality of Life and allow symptomless course for a longer time.

**Keywords**: adrenoleukodystrophy, X-ALD, neurodegenerative disorders, gene therapy

1. INTRODUCTION

Necessity is the mother of invention, as the proverb assigned to Plato proclaims. Scientists can only imagine how great persistence of parents Augusto and Michaela Odone was, who 3 years after the diagnosis of his 6-year old son Lorenzo decided to shake up the research world with invention of Lorenzo’s Oil - at that time the only efficient treatment in delay of the course of his disease. [1]

Adrenoleukodystrophy, X-linked genetic disease, correlated with mutation of ATP-binding Cassette sub-family D Member 1 (ABCD1) gene locus Xq28, was discovered firstly in 1910 by Haberfeld and Spieler, later popularized in 1923 by Siemerling and Creutzfeldt. Both of the teams reported cases of male pediatric patients, previously healthy, whose mental and neurological status started to rapidly deteriorate, developing spastic tetraparesis. Patients died within 8-12 months after the worsening of the clinical state, and histological post mortem examination revealed changes in white matter of the brain along with inflammatory response in CNS. [2] By 1981, the mutation of the X chromosome in locus Xq28 was found to be the cause of the syndrome. In 1987, after several failed treatment options such as eg. unsuccessful bone marrow transplant, Lorenzo’s Oil was introduced to medical world by Prof Moser and the Odones. [3] From 1990s, only few therapeutic options have been introduced, including HSCT and experimental attempts of gene therapy. [4]

Adrenoleukodystrophy (ALD) is a compound of ALD-AMN-adrenoneuropathy, which consists of ALD, adrenomieloneuropathy (AMN) and Schiders syndrome - progressive genetic disorders affecting adrenal glands, spinal cord and myelin sheaths of the neurons. ALD is one of the most common peroxysmal inborn metabolism disease, with about 1:17 000 cases observed in male populations. [5] 55-60% of the X-ALD patients develop AMN-the adult onset of ALD, with neurological motor lesions in limbs due to axonal degeneration of the spinal cord, whereas 35–40% of X-ALD boys develop cerebral ALD (CALD), which leads to early mental regression and death at a young age. [6]

The product of the impaired gene - protein of the apoenzyme lingoceryl-CoA ligase errors in peroxisomal beta oxidation and results in accumulation of impaired structured very long chain fatty acids (VLCFA). This accumulation in adrenal glands results in binding them with cholesterol into hydrolase-resistant esters, significantly reducing the production of steroid hormones. At the same time, the autoimmune reaction causes the demyelination changes in the central nervous system. Increased levels of ACTH produced due to lack of steroid hormones result in increased production of melanocytes and consequently melanin, due to ACTH affinity to MSH biochemical structure. [7]

Current therapeutic strategies which are allowed for widespread use are limited to Lorenzo’s Oil and hematopoietic stem cell transplantation (HSCT), these two options can delay the psychomotor impairment, but cannot treat the direct cause of the disease. Lorenzo’s Oil, a mixture containing glycerol esters of oleic and erucic acid (4 parts of glyceryl troleate, 1 prt of glyceryl trierucate) reduces the amount of VLCFA in serum. Its used along with
dietary restriction - apart from the low VLCFA diet it is necessary to reduce the amount of endogenous VLCFA by providing less harmful fatty acids to the organism. HSCT leads to delay the completion of the inflammation, the auto immune reaction within the white matter of the brain. However, it can be only used in the early stages of the disease, according to the LOES scale of MRI changes, searching for the donor is time consuming, as well as patient may suffer from graft-versus-host disease. [8;9] As for AMN, there is no treatment options available. [10]

<table>
<thead>
<tr>
<th>Symptom type</th>
<th>Male patients</th>
<th>Female patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-symptomatic</td>
<td>Majority in children under 3 years of age with no symptoms, diagnosis with ABCD1 mutation or elevated VLCFA, important follow up for adrenal and cerebral abnormalities</td>
<td>Majority of patients free of symptoms in childhood and early adulthood, demonstration only with elevated VLCFA, ABCD1 mutation, father or children with ALD, risk of symptoms increases with age - from 18% (20-40 years) to nearly 90% in 60 years old patients</td>
</tr>
<tr>
<td>Cerebral manifestations</td>
<td>Behavioral, learning disturbances, seizures, rapidly progressing regression of mental and neurological functions, spastic tetraparesis</td>
<td>Rare, single case reports</td>
</tr>
<tr>
<td>Myelopathy</td>
<td>Mostly in patients with AMN, in course of ALD in adulthood, symptoms of gait disturbance, progressive lower limbs stiffness and sensory disturbances, incontinence</td>
<td>Symptomatic in old age, often misdiagnosed as multiple sclerosis - gait disorder, incontinence, sensory disturbances</td>
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<tr>
<td>Adrenal insufficiency</td>
<td>Often occurring in still neurologically pre-symptomatic cases, primary symptoms starting with muscle weakness, rapid weight loss, low blood pressure, nausea, diarrhea, hypoglycemia, later stages increased skin pigmentation (increased production of melanocytes)</td>
<td>Very rare, single case reports</td>
</tr>
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2. AIM OF THE STUDY

The aim of the study is to review the latest treatment options for adrenoleukodystrophy.

3. MATERIALS AND METHODS

Substantial articles on new treatment of X-ALD options from period 2007-2018 in the Asian, European and American regions have been analyzed. Among 219 articles in PubMed Medline database related to therapy and treatment of X-ALD, 13 articles were selected for analysis and reviewed.

4. RESULTS

Most of the reviewed articles originated in North America (46%), with second large group of European centres involved in X-ALD study (23%).

![Geographical distribution](image)

*Figure 1. Geographical distribution of research. Prepared by authors.*

Among 13 articles, treatment options were divided into two main groups:
- cause-related treatment (11 articles)
- symptoms-related treatment (2 articles)
The “cause-related” treatment group was combined of new therapeutic options for early stages of the disease in order to stop the rapid progression of its course: the attempts of changes on genetic and metabolic level. The “symptoms-related” treatment group consists of articles related to later stages symptoms, such as spasticity or dystonia.

![Pie chart showing distribution of treatment groups.](image)

**Figure 2.** Distribution of treatment groups. Prepared by authors.

![Bar chart showing type of research reviewed.](image)

**Figure 3.** Type of research reviewed. Prepared by authors.
Most common methodology used in reviewed research was cell culturing methods (6 studies), followed by animal studies (4 articles). Case reports and human studies were the minority among found studies.

4. 1. Cause-related treatment

4. 1.1. Pioglitazone treatment

Pioglitazone, medication of thiazolidinedione class, responsible for activation of peroxisome proliferator-activated receptors (PPARs), is one of the effective ways of treatment diabetes melitus type II. It has been associated with stimulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha- PGC-1alpha pathways. Absence of PGC-1 alpha is responsible for mitochondria depletion (in vitro in human neuroblastoma and in vivo in human adipose tissue). The study from 2013 by Morato et al. tried to identify the possible solutions of pioglitazone usage in stimulation of PGC-1 pathways in mice models of X-linked adrenoleukodystrophy. As a result, study showed normalization of mitochondrial biogenesis within DNA/nuclear DNA ratio and increase of mitochondrial proteins NRF1, PGC-1alpha and TFAM. Pioglitazone also helps in normalization of levels of ATP, NADH, and activity of pyruvate kinase, the key enzyme in glycolysis - all sensitive parameters of metabolic failure. The normalization of oxidative stress biomarkers, such as eg. GSA, AASA or MDAL, was proved to decrease, with normalization of glutathione reductase, regardless of the C26:0 levels (which were only slightly decreased within the treatment). The method is also reported to increase mitochondria levels. Lastly, the treatment showed the normal histopathological state, compared to eg. increased GFAP, Lecitin or reduced Cytochrome C and SMI-32 stainings - indicators of axonal degeneration in double knockout group, as well as stopped the progression of locomotor deficits in treadmill and bar cross tests. [5]

4. 1.2. Resveratrol or transgenic activation of sirtuin-1

Next study by Morato et al. from 2015 tried to indicate the benefits of activation of sirtuin-1 as a mean of treatment of ALD. Sirtuins, deacetylases highly NAD+-dependent, promote the production of new mitochondria with nuclear respiratory factors (NRFs) and mitochondrial respiratory factor A (TFAM). Sirtuin-1 (SIRT-1), the most described enzyme can be stimulated with compounds such as resveratrol (RSV), a natural phenol produced by flora after an injury or pathogens invasions, used as a dietary supplement. In the study, the similar comparisons regarding mitochondrial biogenesis, normalization of metabolic failure and oxidative stress biomarkers, as well as histopathological and behavioral positive changes proved the efficiency of SIRT-1 stimulation with RSV or transgenic overexpression, were performed. Sirtulin activation also supported the mitochondrial function, which was observed with prevention of impaired mitochondrial oxidative phosphorylation. [11]

4. 1.3. Polysialylated Form of Neural Cell Adhesion Molecule-Positive Cells (PSA-NCAM+)

The transplantation of exogenous cells to supply the impaired myelin production is a noveau and experimental approach, performed mostly on cell cultures. The 2013 study of Jang J. et al, confirmed that the precursors of oligodendrocytes, PSA-NCAM+ cells, are stimulated into glial growth with triiodothyronine (T3). Thyroid hormone induces ABCD2 expression in those cells by 1.8 fold than in untreated controls. ABCD 2 gene is related to
gene of ABCD1, therefore, this feature can be used in future correction of the X-ALD defect within transplantation of those cells and replacement of impaired glia. [12]

4. 1. 4. Gene therapy - adeno-associated virus serotype 9

Gene therapy is described as therapeutic delivery of nucleic acid into patient cells in order to treat the disease. Modification of human DNA is supposed to treat until now incurable predispositions and diseases coded in our genes. The DNA proper gene, provided with a vector to the impaired gene cell, is considered as a drug for the disease. [13] The 2015 study by Gong et al. decided to measure in vitro and in vivo on mice models the possibility to treat X-ALD with the gene therapy means. As a vector, recombinant adeno-associated virus 9 (rAAV9) was chosen due to its ability to bypass blood-brain barrier and target cells of the central nervous system. The study proved the efficiency of in vitro expression in brain cell cultures after rAAV9 transduction of the ABCD-1 gene, which expressed mostly in astrocytes (84%) - success was measured with the significant reduction of C26:0 levels and C26/24 C26/22 ratios after the treatment, with no signs of cytotoxicity. Within in vivo injection both with intracerebroventricular (ICV) and intravenous (IV) injections, the ICV injection showed more focal distribution of the gene, whereas IV approach proved to distribute more evenly the gene in the CNS. The differences occurred also in cell types targeted - ICV targeted mainly astrocytes, microglia and neurons, whereas IV targeted also oligodendrocytes and microvascular endothelial cells. Since the risk of local inflammation after ICV injection means more damaging consequences in X-ALD patients, as well as the lack of possibility of secretion of the ABCD1 gene, more safe and reasonable in distribution would be the future IV course of this treatment. [10]

4. 1. 5. Hematopoetic Stem Cell Gene Therapy

The variation of the hematopoetic stem cell transplantation with gene therapy has been introduced by Eichler et al. in 2017 study. The total group of 17 patients received infusion of autologous CD34+ cells transduced with the elivaldogene tavalentivec (Lenti-D) lentiviral vector - adrenoleukodystrophy ABCD1 gene cDNA-specifying vector clone. After 24 months, 15 of 17 (with 2 withdrawals from the treatment due to rapid progression or allogeneic stem-cell transplantation) had no major functional disability, minimal clinical symptoms and no signs of clonal outgrowth post-transplantation. The important aspect discussed is the necessity of further assessment of long-term outcomes and safety, however the treatment is shown to be an effective alternative to patients in early stage of the disease. [14]

4. 1. 6. ABCD2 induction - caffeic acid phenethyl ester (CAPE) and suberoylanilide hydroxamic acid (SAHA)

The overexpression of other ABCD genes - ABCD2 and 3 demonstrates compensation of the ABCD1 deficiency, and this overexpression can be achieved with histone deacetylase inhibitors. [15;16] The 2013 study by Singh et al. examined the therapeutic option of CAPE, natural flavonoid. This component of honeybee propolis is a histone deacetylase (HDAC) inhibitor of carboxylic acid class, which together with its anti-inflammatory activity, antioxidative, lipid peroxidation inhibition potential and blood-brain barrier bypass properties make it a good compound for further study. The research was conducted on human skin fibroblasts and mouse primary mixed glial cells. Results confirmed induction of
ABCD2/ABCD3 mRNA expression and consequent increase of beta-oxidation of human skin fibroblasts in peroxisomes and mitochondria, which led to the decrease of VLCFAs and normalization of the biochemical parameters. In mouse glial cells, the increase of ABCD2 expression was noted in astrocytes and oligodendrocytes, consequently with increased beta-oxidation and interestingly, the inhibition of the elongase ELOVL-1, which plays a significant role in elongation of the fatty acids chains. [17]

Similar approach has been undertaken in 2015 study from the same center by Baarine et al. In this research, SAHA as HDAC inhibitor was examined from perspective of correction of mitochondrial disfunctions within: increase of antioxidant activity, increase of ATP levels and correction of mitochondria transmembrane potential. In addition to previous studies which proved the upregulation of ABCD2 with SAHA, as well as normalization of beta-oxidation and reduction of VLCFA levels, this research confirmed the positive influence of SAHA to improving mitochondrial functions in ALD models of rat B12 oligodendrocytes and human U87 astrocytes. [18, 19]

4. 1. 7. ABCD2 in lymphocytes and monocytes - induction with retinoic acid (RA)

Lymphocytes and monocytes play an important role in induction of inflammatory response to the pathological changes in ALD. Retinoic acid, metabolite of vitamin A, affects the development of immune system as well as has anti-inflammatory characteristics, and is primarily used in dermatological diseases. It has been confirmed that RA is able to induce ABCD2 expression in vitro. [20] Therefore, the 2014 study by Weber et al. tried to find the possible solutions of ABCD2 stimulation both in vitro (THP-1 a human monocyte/macrophage-like suspension cell line) and in vivo (monocytes from blood of patients with acne, without ALD, treated with Isotretinoin). In this study, the in vivo ABCD2 mRNA expressions remained unchanged compared with pretreatment results, in vitro - the fourfold induction of ABCD2 expression is still considered an insufficient level, comparing to ABCD1 levels in healthy controls. [21]

4. 2. Symptoms-related treatment

4. 2. 1. Intrathecal baclofen treatment for X-ALD related spasticity

Baclofen is a muscle relaxant used in treatment of multi-drug resistant spasticity in spinal cord injuries or MS, believed to activate GABA-beta receptors. Intrathecal baclofen pump is a device - a catheter providing medication to the spinal fluid, and a pump placed under abdomen skin, consisting of microprocessor, battery and medication reservoir, which has to be refilled every 1-6 months. 2016 study by Hjartarson et al. Reported successful baclofen treatment of X-ALD related spasticity in 2 cases of pediatric ALD patients, with positive effects sustained within months after implementation. [22]

4. 2. 2. Deep Brain Stimulation in X-ALD secondary dystonia

Deep Brain Stimulation (DBS) is an operation involving the stimulation of brain structures responsible for motor disorders in psychiatric diseases by means of a special device, called the "brain pacemaker". The operation consists of setting up the stimulation catheter to the specific regions of the brain and generator placed in sub-clavicular fossa, responsible for stimulating those areas. [23] Since 2002 is one of the treatments for Parkinson's disease, recently also experimentally used in Tourette's syndrome. [24] Since it
has been successfully effective in secondary dystonias in other inborn errors of metabolism, a study by Karnebeek et al. from 2014 reported the attempts of treatment of dystonia related to X-ALD in 18-year old patient with the use of DBS. After 25 months, there was no significant improvement in course of dystonia with scores of Burke-Farn-Mardsen: pre-65.5, post-62, and disability scores: pre-28 and post-26, respectively before and after induction of the treatment. Following the DBS, dantrolene was administered for reduction of spastic changes, where the improvement was shown in increased flexibility of right upper limb and lower limbs. [6]

5. CONCLUSIONS

Presented research shows progress in treatment options for X-ALD. Gene therapy, variations of hematopoetic stem cell transplantation as well as research within known and used substances in medicine, such as pioglitazone, give hope to the patients for more effective ways of treatment in the nearest future, in order to prolong progression-free survival period. However, this research is still in primary in vitro and animal tested stages, therefore it will surely take much more time to provide answers to further questions, created with those temporary hopes. On the other hand, the treatment of secondary neurological symptoms is still awaiting for better solutions for ALD patients, as well as patients of other neurodegenerative disorders, in order to improve their Quality of Life and allow symptomless course for a longer time.

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