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Allan-Herndon-Dudley-Syndrome in Childhood: Is there No Cure?

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

The syndrome, first described in 1944 by William Allan, Florence C. Dudley, and C. Nash Herndon, is a syndrome which results of disturbed formation of two thyroid hormone transporters, MCT8 and Oatp1c1. Nearly 320 individuals of 132 families have been described with MCT-8 deficiency. Since the first individual treatment attempt with LT4 and Propylthiouracil in 2008, the development of therapies for Allan-Herndon-Dudley syndrome (AHDS) has gained momentum in recent years. Treatment strategies range from symptomatic interventions including botulinum toxin injections, levodopa/carbidopa, assistive devices, functional therapies, rehabilitation to replacement therapies (LT3, LT4, DIPTA, TRIAC, TETRAC), and gene therapy. The diagnosis, treatment and cure of Allan-Herndon-Dudley syndrome in childhood remains challenging for the future.

Keywords: MCT8; child; thyroid transporter-analogon; treatment; genetics.

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1. INTRODUCTION

“First described in 1944 by William Allan, Florence C. Dudley, and C. Nash Herndon, where they described a misfunction of two thyroid hormone transporters” [1,2]. “More then 100 families and more then 300 individuals were described in the literature to date” [1,3-22]. “There is an unknown incidence of involved cases to date due to the small population [3]. Males are primary included, only a few female cases have been described so far” [4,5]. The disease includes symptoms like congenital hypotonia, most often found at birth or in the first weeks after delivery, which shows progressive states to spasticity with contractures, Babinski sign is early detected in life. Hyperreflexia will be found later in life [1,3-22]. Affected male patients exhibit muscle hypoplasia and muscle weakness in early childhood, resulting in disturbances of head control and motor milestones, which are found to be delayed [3]. In nearly all patients hypotonia and severe intellectual deficits are found [3]. “Psychomotor disturbances are found from delivery, a delay in motor and speech milestones and autonomal function is never achieved.

The facial impression has characteristic features that starts and ameliorate over time: open mouth situation, tense upper lip, ptosis of the left or right eye, abnormal ear folding, thickening of soft tissues of the nose and ears, and deformed or rotated earlobes” [3,23]. “Long, thin, everted feets are also typically found in many patients. Rotatory nystagmus and disconjugate eye movements are rare features in the eyes. Some patients can develop seizures and poor weight gain with low weight percentiles. Pectus excavatum and scoliosis manifestations are also infrequently present, as a result of hypotonia and muscle hypoplasia. AHDS is induced most often by mutations in the SLC16A2 gene (Xq13.2), which encodes the monocarboxylate transporter 8 (MCT8), a transporter for thyroid hormone T3. The causative mutations show chain terminations, deletions preserving the reading frame, also nonsense and missense mutations. Neurological problems occur due to the functional loss to transport the thyroid hormone T3 into special neuronal cells.

Clinical findings reveal the diagnosis and normal and altered thyroid hormone found in serum: male patients have high 3,3',5'-triiodothyronine (T3) levels, low to normal free tetraiodothyronine (T4) levels, and normal to mildly elevated TSH levels, but sometimes low TSH, which is found to be unexpected” [6]. “A few countries focus on inclusion into the newborn screening” [7]. “A molecular analysis shows mutations in the SLC16A2 gene, and this, confirms the diagnosis of AHDS” [3]. Differential diagnoses focus on diseases with X-linked intellectual disability associated with ataxia, spastic paraplegia, muscle hypoplasia, X-linked intellectual disability with spastic paraplegia and iron deposition, X-linked progressive cerebellar ataxia and spastic paraplegia type 2.

Snyder-Robinson syndrome or Pelizaeus-Merzbacher disease should also be focused on [8,9,10,11]. Prenatal diagnosis is thinkable in families if a disease-causing mutation has been clearly ruled out. The way of transmission is X-linked recessive. Genetic counseling should be offered to affected families to identify carriers of an SLC16A2 mutation. Currently, there is no treatment for the disease, only supportive therapy is helpful but not curative. Physiotherapy, occupational therapy, and language therapy can be helpful in any way. Dystonic episodes can be treated with different medications, anticholinergics, L-DOPA, carbamazepine, and baclofen therapy. Antiepileptic drugs can help to control seizures. Treatment of hypothyroidism is not helpful. Concerning survival, some patients have survived into their 60s. The overall life expectancy is delayed, and quality of life is restricted. Most patients are unable to sit, stand, or walk independently.

1.1 Empirical Review

The rare syndrome, first described in 1944 by William Allan, Florence C. Dudley, and C. Nash Herndon, shows an impaired formation of two thyroid hormone transporters [1]. The result is the inability of nerve cells, which rely on thyroid hormones, to uptake these important hormones into cells. Allan-Herndon-Dudley syndrome, is characterized in male patients and to date only few females by neurological symptoms with hypotonia and feeding problems in newborn period, developmental disturbances and intellectual delay ranging from mild to profound and late-onset or occuring pyramidal signs [4,5,24]. Extrapyramidal symptoms like dystonic movements, choreoathetotic movements, paroxysmal movement disorder, hypokinesial states, masked facial impressions and seizures, often with drug resistance were present. Approximately 320 patients with a pathological variant in SLC16A2 have been described in published world literature [1,3-31]

Additional symptoms can include dysthyroidism, showing as poor weight gain, low muscle mass, and varying cold intolerance, sweating, tachycardia, and irritability and pathognomonic thyroid tests. Many female heterozygous patients are not clinically ill but can have minimal thyroid test abnormal results [4,5]. AHDS can be found mostover in male patients but also in few cases, in females, like stated above [4,5]. One female teenager showed the typical features of AHDS and primary ovarian insufficiency in a case report description [5]. In another case reports, frameshift variants were described [11]. A 2-year-old Japanese child was diagnosed with MCT8 deficiency according to a new frameshift variant, identified as NM_006517.5(SLC16A2_v001): c.966dup [p.(Ile323Hisfs*57)] variant [11]. The child, a male patient, showed serious developmental disturbances, with no head muscular control and inability to speak words with a clear meaning [12]. Missense or in-frame mutations of SLC16A2 result normally in milder symptoms and late-onset pyramidal signs, loss-of-function mutations are described to have more severe clinical manifestations [12]. Variants which include an intracellular C-terminal tail of MCT8 were described as not harmful unless they found frameshifts that lengthen the MCT8 protein signifantly [12]. This information seems to give clinical advice on evaluating the significance and importnace of variants in the C-terminal domain of MCT8 [13]. MCT8 deficiency includes severe locomotor and psychomotor disturbances due to inadequate TH transport across molecular brain barrier and interfered neural TH action [14]. In a mice study, Mct8/Oatp1c1 double knockout (DKO) mice served as an animal model for MCT8 deficiency, showing in detail central TH deprivation, locomotor delay, and similar histomorphological features as MCT8 patients [15]. The mechanisms behind these neurological and motoric symptoms are not ruled out and clearly understood in detail. In this upper mentioned study, a special proteome analysis of different brain sections from 21-day-old WT and DKO mice was performed, with identification of over 2900 different proteins with the technique of liquid chromatography mass spectrometry [15]. 67 of 2900 proteins revealed significant differences between the individual genotypes [15]. When comparing the proteomic and RNA-sequencing analysis data, a significant overlap in alterations were detected [15]. Consistent with previous scientific results, DKO mice showed reduced myelin-associated protein expression and differences in levels of established neuronal TH-regulated targets [15]. A decreased protein and mRNA expression of Pde10a, an enzyme found in the striatum, crucial for dopamine receptor signaling, in DKO mice, was present [15].

Changes in PDE10A activities are relating with dystonic problems, supposing that reduced basal ganglia PDE10A expression may be a important key pathogenic pathway in human MCT8 deficiency [15].

Normal CNS myelination depends on the timely availability of thyroid hormone (TH) to support the differentiation of oligodendrocyte precursor cells (OPCs) into mature cells, the group of myelinating oligodendrocytes [16]. Allan-Herndon-Dudley syndrome, induced by mutations in the TH transporter MCT8, often presents with abnormal myelination [16,30,32]. An important study including Mct8/Oatp1c1 double knockout (Dko) mouse model, which mimics MCT8 deficiency in human beeing and has lower TH transportation across molecular brain barriers, shows persistence of hypomyelination as an important CNS feature [16].

The collaborators investigated, whether the decreased myelin content in Dko mice is due to impaired oligodendrocyte maturation [16]. “OPC and oligodendrocyte populations were classified in Dko mice, wild-type mice, and single TH transporter knockout mice at different developmental phases (postnatal days P12, P30, and P120) using multi-marker immunostaining and confocal microscopy” [16]. “Only in Dko mice researchers found a decrease in cells expressing the oligodendroglia marker Olig2, spanning all stages from OPCs to mature oligodendrocytes” [16]. “Dko mice showed an elevated population of OPCs and a lower number of mature oligodendrocytes in both white and grey matter areas at all time points, resuming a blockage in differentiation in the absence of Mct8/Oatp1c1” [16]

Cortical oligodendrocyte structural parameters by quantifying the number of mature myelin sheaths per oligodendrocyte were analyzed. A decrease in myelin sheaths, which were longer in length, were only present in Dko mice suggesting a compensatory response to the reduced number of mature oligodendrocytes [16]. These mechanisms revealed a relation between abnormal myelination state and compromised neuronal function in Mct8/Oatp1c1 deficient animals [16].

1.2 Descriptive Review

A multidisciplinary team approach should give standard care informations for hypotonia, poor feeding, developmental delay/intellectual disability, spasticity, and extrapyramidal movement disorders.

Anticonvulsive medication should be administered by a qualified neurologic pediatrician. Thyroid hormone replacement therapy during childhood is not recommended in AHDS to date as it may worsen a situation of dysthyroidism. Children should be checked clinically every six months until the age of four years, then annually for developmental progress or delay, educational support, neurologic disturbances, spine and hip joint analysis, and mobility/self-help skills. Limited therapeutic medications and skills are currently available for treating the disease, with the main focus being on ameliorating the thyrotoxic situation rather than neurological symptoms. Research focus on thyroid hormone analogon like TRIAC [2,27], DITPA, and TETRAC [18-22], which can potentially ameliorate normal organ function without the need for MCT8. Other therapeutic approaches, such as gene replacement therapy and pharmacological chaperones, are also being in research to ameliorate the transport of thyroid hormones through MCT8. Two types of treatment have been studied in MCT8 deficiency. The first involves normalizing serum T4 and T3 levels using a "block-and-replace" approach with Propylthiouracile and T4 hormone [17]. Treatment of older AHDS patients did not show significant neurological improvement but did have positive effects on body weight, heart rate, and certain blood markers. These changes are attributed to reduced exposure of peripheral tissues to high serum T3 levels. It is possible that neurological benefits may only be seen if this treatment is started soon after birth. Another potential treatment option is the use of a *thyroid hormone analogue* that can enter the brain independently of MCT8 [18,19,20]. Following promising results in MCT8 KO mice with diiodothyropropionic acid (DITPA), a clinical trial was conducted with this analogue in four younger AHDS patients. While this treatment normalized serum T4 and T3 levels and had positive effects on peripheral tissues, including weight gain and heart rate reduction, there was no significant neurological improvement. DITPA has low affinity for T3 receptors, so the thyroid hormone metabolite TRIAC may be a better option for MCT8 patients. TRIAC has several advantages, including high affinity for T3 receptors, independent cellular uptake, metabolism by DIO3, proven activity in brain cells, availability, and clinical experience in other conditions [18-20]. A multicenter trial is currently investigating the potential benefits of TRIAC treatment in MCT8 patients. Recent studies suggest that treatment with the TRIAC precursor TETRAC may also be beneficial for MCT8 patients [21,22]. TETRAC allows for the regulation of brain TRIAC levels through DIO2-mediated production [21,22]. However, there is less clinical experience with TETRAC and it is not readily available [21,22].

2. CONCLUSIONS

The treatment options of MCT8 deficiency or AHDS focus on analyzing the specific symptoms present in each individual. Prenatal treatment approaches were performed [26]. A multidisciplinary team approach of specialists, including pediatric neurologists, pediatric surgeons, pediatric orthopaedists, language pathologists, physical therapists, and other healthcare professionals, may collaborate to elaborate and implement a comprehensive treatment approach for affected individuals. Clinical trials and studies focus on potential treatments for MCT8 deficiency. The combination of propylthiouracil (PTU) and L-thyroxine (L-T4) has been shown to improve nutritional status. Other treatments being investigated include thyroid hormone analogues, phenylbutyrate [22], and gene therapy approaches, though these are still in the experimental stages and childhood shoes and not yet available for widespread use to date. Early diagnosis and the development of an effective treatment plan will be crucial in addressing the severe symptoms seen in affected individuals. An association with ganglioglioma, intermittent esotropia in 4 siblings and sensineural hearing loss were described [24,28,30].

Concerning genetic counseling aspects, AHDS is inherited in an X-linked way. If the mother of a proband has a pathogenic variant in the SLC16A2 gene, there is a 50% chance of transmitting it in each pregnancy. Males who inherit the variant will be affected, while females who inherit it will be carriers and typically not show clinical symptoms, though they may have minor thyroid test abnormalities. Once the pathogenic variant in SLC16A2 has been identified in a family member, carrier testing for at-risk female relatives, prenatal testing for

pregnancies at increased risk, and preimplantation genetic testing are options.

A description of characteristics of MCT8 deficiency in a large dutch patient cohort revealed poor survival with a high prevalence of treatable underlying risk factors, and provides knowledge that might inform clinical management and future evaluation of therapies [3]. In conclusion, Allan-Herndon-Dudley syndrome is a very rare disease in childhood and there are only few effective treatment options. Like in many other genetic rare diseases, a one-time gene therapy approach would be desirable to cure the disease, but this is, to date, in childhood shoes. Due to the low number of population, bigger studies are difficult to establish to find clear guidelines of this extreme rare disease in childhood.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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