Review Article

Allan-Herndon-Dudley-Syndrome in Childhood: Is there no cure?

Abstract
The syndrome, first described in 1944 by William Allan, Florence C. Dudley, and C. Nash Herndon, is a result 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

Introduction
First described in 1944 by William Allan, Florence C. Dudley, and C. Nash Herndon, the syndrome is a result of impaired formation of two thyroid hormone transporters [1]. At least 132 families with 320 affected individuals have been described in the literature so far [1-21]. Although the prevalence is unknown, a study identified AHDS in 1.4% of men with intellectual disability of unknown etiology [2]. Mostover males are affected, only few cases in females have been published [3,4]. The disease manifests as congenital hypotonia, present at birth or in the first weeks/months of life, which progresses to spasticity with contractures, Babinski sign and clonus and is usually detectable early in life. Hyperreflexia occurs later in life [1-21]. Affected males also exhibit muscle hypoplasia and generalized muscle weakness in infancy and early childhood, resulting in difficulties supporting the head and delayed motor milestones [2]. Hypotonia and severe intellectual deficits are present in 100% of patients [2]. Severe psychomotor delays are present from the beginning, a delay in motor and language milestones and autonomy is never achieved. The face has characteristic features that develop over time: open mouth, tense upper lip, ptosis, abnormal ear folding, thickening of soft tissues of the nose and ears, and upwardly rotated earlobes [2]. Long, thin, everted feet are also typical. Eye manifestations like rotatory nystagmus and disconjugate eye movements are rare. Some patients may experience seizures and poor weight gain. Pectus excavatum and scoliosis are sometimes present, possibly as a result of hypotonia and muscle hypoplasia. AHDS is caused by mutations in the SLC16A2 gene (Xq13.2), which encodes the monocarboxylate transporter 8 (MCT8), a specific transporter for the thyroid hormone T3. The identified mutations include chain terminations, deletions preserving the reading frame, as well as nonsense and missense mutations. Neurological problems may be due to the inability to transport the thyroid hormone T3 into some neuronal cells. The diagnosis is based on clinical findings and normal and altered thyroid hormone serum levels: males have abnormally high 3,3',5'-triiodothyronine (T3) levels, low to normal free tetraiodothyronine (T4) levels, and normal to slightly elevated TSH levels, but sometimes unexpected low TSH [5]. A few countries focus on inclusion into the newborn screening [6]. A molecular genetic test showing mutations in the SLC16A2 gene confirms the diagnosis [2]. Differential diagnoses include conditions with X-linked intellectual disability associated with ataxia, spastic paraplegia, or muscle hypoplasia, e.g., X-linked intellectual disability with spastic paraplegia and iron deposition, X-linked progressive cerebellar ataxia and spastic paraplegia type 2. Pelizaeus-Merzbacher disease and Snyder-Robinson syndrome should also be considered [7,8,9,10]. Prenatal diagnosis is possible in affected families if a disease-causing mutation has been identified. 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 AHDS, and management consists of supportive measures. Physiotherapy, occupational therapy, and speech therapy may be helpful. Dystonia can be treated with certain medications, including anticholinergics, L-DOPA, carbamazepine, or baclofen. Seizures, if present, can be controlled with standard antiepileptic drugs. Treatment of hypothyroidism does not appear to be

beneficial. Although some patients have survived into their 60s, overall life expectancy is impaired, and quality of life is severely restricted as most patients are unable to sit, stand, or walk independently.

Empirical Review

The syndrome, first described in 1944 by William Allan, Florence C. Dudley, and C. Nash Herndon, is a result of impaired formation of two thyroid hormone transporters [1]. This leads to the inability of nerve cells, which rely on thyroid hormones, to uptake them. Allan-Herndon-Dudley syndrome, an X-linked disorder, is characterized in males and a few females by neurologic findings with hypotonia and feeding difficulties in infancy, developmental delay and intellectual disability ranging from mild to profound and later-onset pyramidal signs [3,4]. Extrapyramidal findings like dystonia, choreoathetosis, paroxysmal movement disorder, hypokinesia, masked facies and seizures, often with drug resistance were described. To date, approximately 320 individuals with a pathogenic variant in SLC16A2 have been documented in published literature [1-30] Additional findings can include dysthyroidism, manifested as poor weight gain, reduced muscle mass, and variable cold intolerance, sweating, elevated heart rate, and irritability and pathognomonic thyroid test results. Most heterozygous females are not clinically affected but may have minor thyroid test abnormalities [3,4]. AHDS can be found most often in male gender but also in few cases, in females [3,4]. One female teenager showed the typical features of AHDS and primary ovarian insufficiency [4]. In another case reports, frameshift variants were described [11]. A 2-year-old Japanese boy was diagnosed with MCT8 deficiency due to a new frameshift variant, classified as NM_006517.5(SLC16A2_v001): c.966dup [p.(Ile323Hisfs*57)] variant [11]. The boy exhibited severe developmental delay, with no head control and inability to speak meaningful words [11]. While missense or in-frame mutations of SLC16A2 typically result in milder symptoms and later-onset pyramidal signs, loss-of-function mutations are associated with more severe clinical manifestations [11]. Variants that impact the intracellular C-terminal tail of MCT8 were probably be described as not harmful unless they result in frameshifts that lengthen the MCT8 protein [11]. These results seem to offer clinical advice on evaluating the significance of variants in the C-terminal domain of MCT8 [12]. MCT8 deficiency leads to severe locomotor and psychomotor disabilities due to inadequate TH transport across brain barriers and compromised neural TH action [13]. In an animal study, Mct8/Oatp1c1 double knockout (DKO) mice served as an animal model for this disease, showing central TH deprivation, locomotor impairments, and similar histo-morphological features as MCT8 patients [14]. The mechanisms behind these neuro-motor symptoms are not well understood. In this study, a proteome analysis of brain sections from 21-day-old WT and DKO mice was conducted, identifying over 2900 proteins with liquid chromatography mass spectrometry [14]. 67 proteins showed significant differences between the genotypes [14]. Comparison of the proteomic and RNA-sequencing data revealed a significant overlap in alterations [14]. Consistent with previous findings, DKO mice exhibited reduced myelin-associated protein expression and changes in levels of established neuronal TH-regulated targets [14]. A decreased protein and mRNA expression of Pde10a, a striatal enzyme crucial for dopamine receptor signaling, in DKO mice, was found [14]. Altered PDE10A activities are associated with dystonia, suggesting that reduced basal ganglia PDE10A expression may be a key pathogenic pathway in human MCT8 deficiency [14]. Proper CNS myelination relies on the timely availability of thyroid hormone (TH) to promote the differentiation of oligodendrocyte precursor cells (OPCs) into mature, myelinating oligodendrocytes [15]. Allan-Herndon-Dudley syndrome, caused by inactivating mutations in the TH transporter MCT8, often presents with abnormal myelination [15]. Similarly, a study including Mct8/Oatp1c1 double knockout (Dko) mouse model, which mimics human MCT8 deficiency and has reduced TH transport across brain barriers, shows persistent hypomyelination as a prominent CNS feature [15]. In this study, the collaborators investigated, whether the decreased myelin content in Dko mice is due to impaired oligodendrocyte maturation [15]. OPC and oligodendrocyte populations were studied in Dko mice, wild-type mice, and single TH transporter knockout animals at different developmental stages (postnatal days P12, P30, and P120) using multi-marker immunostaining and confocal microscopy [15]. Only in Dko mice researchers observed a decrease in cells expressing the oligodendroglia marker Olig2, spanning all stages from OPCs to mature oligodendrocytes [15]. Additionally, Dko mice showed an elevated proportion of OPCs and a reduced number of mature oligodendrocytes in both white and grey matter regions at all time points, indicating a blockage in differentiation in the absence of Mct8/Oatp1c1 [15] Cortical oligodendrocyte structural parameters by quantifying the number of mature myelin sheaths per oligodendrocyte were evaluated. Only Dko mice exhibited a decrease in myelin sheaths, which were longer in length, suggesting a compensatory response to the reduced number of mature oligodendrocytes [15]. The findings of this animal study revealed an impairment in oligodendrocyte differentiation and altered oligodendrocyte structural parameters in the absence of Mct8 and Oatp1c1 [15]. These mechanisms likely contribute to the abnormal myelination state and compromised neuronal function in Mct8/Oatp1c1 deficient animals [15].

Descriptive review

A multidisciplinary team should provide standard care for hypotonia, poor feeding, developmental delay/intellectual disability, spasticity, and extrapyramidal movement disorders. Anti-seizure medication should be administered by a qualified neurologist. Thyroid hormone replacement therapy during childhood is not recommended as it may worsen dysthyroidism. Children should be evaluated every six months until

age four, then annually for developmental progress, educational needs, neurologic changes, spine and hip health, and mobility/self-help skills. Limited therapeutic options are currently available for treating the condition, with the main focus being on improving the thyrotoxic state rather than neurological symptoms. Research is being conducted on thyroid hormone analogs like TRIAC, DITPA, and TETRAC [17-21], which can potentially restore normal organ function without the need for MCT8. Other approaches, such as gene replacement therapy and pharmacological chaperones, are also being explored to enhance 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 PTU and T4 [16]. 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 [17,18,19]. 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 [17-19]. 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 [20,21]. TETRAC allows for the regulation of brain TRIAC levels through DIO2-mediated production [20,21]. However, there is less clinical experience with TETRAC and it is not readily available [20,21].

Conclusions

The treatment of MCT8 deficiency focuses on addressing the specific symptoms present in each individual. A multidisciplinary team of specialists, including pediatricians, surgeons, neurologists, orthopedists, speech-language pathologists, physical therapists, and other healthcare professionals, may collaborate to plan and implement a comprehensive treatment approach for affected children. Clinical trials and studies are exploring potential treatments for MCT8 deficiency. The combined use of propylthiouracil (PTU) and L-thyroxine (L-T4) has been suggested to improve nutritional status. Other treatments being investigated include thyroid hormone analogues, phenylbutyrate, and gene therapy, though these are still in the experimental stages and not yet available for widespread use. Early diagnosis and the development of an effective treatment plan will be crucial in addressing the severe symptoms seen in affected individuals. Concerning genetic counseling aspects, AHDS is inherited in an X-linked manner. 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 [2]. 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.

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