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CASE REPORT

Report of a severe case of Allan-Herndon-Dudley syndrome

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Abstract

Allan-Herndon-Dudley syndrome (AHDS) is an X-linked neuromuscular disorder characterized by psychomotor retardation, intellectual disability, muscular hypotonia, feeding difficulties and neurological symptoms in boys.1 Diagnosis is mainly made through molecular genetic testing where a proband is established with relevant clinical findings and a pathogenic variant in hemizygosis in the *SLC16A2* gene. We will describe the case of a 3-year-old boy who was initially referred to the medical genetics service to rule out trisomy 21, with significant global neurodevelopmental delay, severe hypotonia, recurrent respiratory infections, poor weight gain, reduced muscle mass, seizures, dysphagia, chronic constipation, among others. Implying a challenging management due to the complexity of the symptoms. A heterozygous pathogenic variant in the *SLC16A2* gene, clinically unaffected, was identified in the mother.

INTRODUCTION

Allan-Herndon-Dudley syndrome (AHDS) is an X-linked neuromuscular disorder, evidenced in males with neurological signs, dysthyroidism and craniofacial findings, characterized by hypotonia, feeding difficulties, neurodevelopmental delay, mild to profound intellectual disability, extrapyramidal signs, athetoid movements, pyramidal signs, seizures that are sometimes late and resistant to medication, extrapyramidal signs, athetoid movements, pyramidal signs and seizures that are sometimes late and resistant to medication, neurodevelopmental delay, mild to profound intellectual disability, extrapyramidal signs, athetoid movements, pyramidal signs, seizures that are sometimes late and resistant to medication, and spastic paraplegia, among others [1]. Poor weight gain, cold intolerance, irritability, sweating, tachycardia, muscle hypoplasia, among others, are also observed. Less severe manifestations can also be observed with minor craniofacial dysmorphias such as palpebral ptosis, low implantation of the auricular pavilions and ajar mouth.

Laboratory findings include normal or slightly elevated serum TSH levels, low or low-normal total T4 and free T4 concentrations, high free T3 and low reverse T3 [2]. Brain MRI usually shows myelination disorder that sometimes improves over the years. Brain atrophy is a frequent sign also associated with hypomyelination [3].

The disease is diagnosed in the index case by molecular genetic testing where a pathogenic variant in the *SLC16A2* gene, which codes for the thyroid hormone transporter (Mct8 transporter), is identified in the brain and other tissues [4]. Since these hormones play a critical role in neurodevelopment, alterations in their transport can have serious repercussions on cognitive and motor development [5].

Despite its monogenic nature, the disease exhibits considerable phenotypic variability, both inter- and intra-familial. This article describes a severe case of SAHD in a 3-year-old male

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patient, exhibiting a complex clinical presentation and confirmed by exome sequencing. Carrier status of the pathogenic variant in the mother was also confirmed, which has important implications for genetic counseling of the family [1,3,6].

METHODOLOGY

Double-stranded DNA capture primers against approximately 36.5 Mb of the human exome (targeting >98% of Ref-Seq coding regions based on the GRCh37/hg19 genome version) were used to enrich regions of interest from genomic DNA fragments using the Twist Human Core Exome Plus kit. The generated library is sequenced on an Illumina platform to a read depth of at least 20x for 98% of the target bases.

A proprietary bioinformatics method was applied including alignment of reads with the GRCh37/hg19 reference version of the human genome, variant annotation and filtering. The evaluation of variants focuses on those located in exons and flanking +/-20 bp intronic regions with clear gene-phenotype relationship (according to OMIM).

All possible inheritance patterns were considered. In addition, the patient's clinical information and family history were used to evaluate the identified variants for pathogenicity and causality. All variants associated with the patient's phenotype were reported. Quality criteria and validation of astringent processes for variant detection by NGS were established. Variants with low quality and/or uncertain zygosity were confirmed by alternative methods.

CASE PRESENTATION

Male patient 3 years old, son number 6 of mother 29 years old (G6P0A3C3) and father 34 years old, not consanguineous. During her gestation, she underwent regular prenatal check-ups, with the eventuality of presenting during the first trimester asthma crisis, severe anemia that required two transfusions, fever secondary to urinary tract infection and vaginal infection, both of which were treated.

Cesarean section was performed for previous cesarean section at 39 weeks of gestational age. The baby had a normal cry at birth with a birth weight of 2.6 kg and required hospitalization for early neonatal sepsis for 3 days.At 2 months of life, there was evidence of significant hypotonia, which progressed to difficulty in feeding and poor weight gain. The patient's clinical condition has remained without any progress or autonomy in spite of the therapies and medical interventions received to date.Psychomotor Development.

Currently the patient at 3 years of life shows a significant psychomotor delay: no head support, does not roll over, does not sit, does not crawl, does not walk and inability to express himself verbally (see Figure 1 & 2).

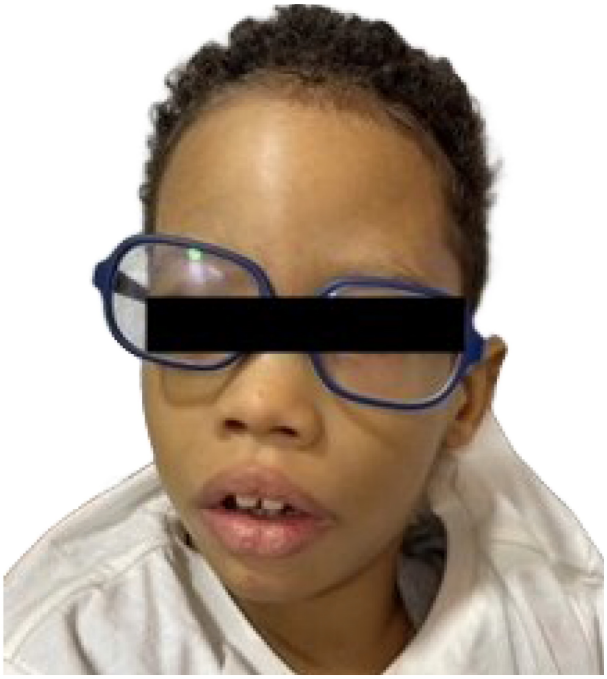
Heredofamilial history

* Asthmatic mother.* Older brother died without diagnosis at 1 month and 24 days of life.

Figure 1. Patient's facies and inability to sit up.

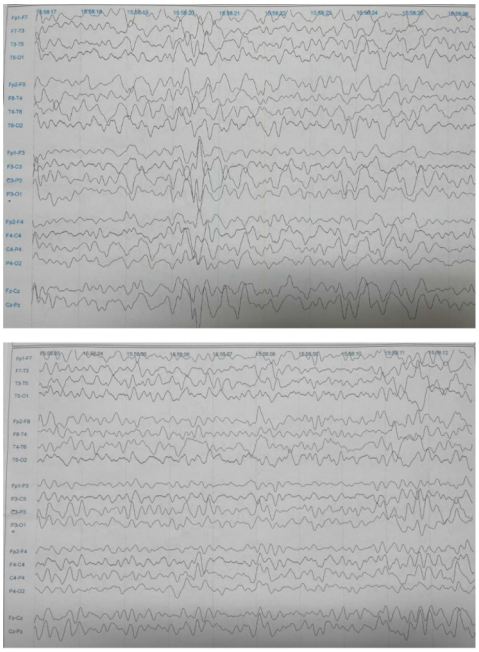
Patient is unable to sit independently, needs support from his mother to maintain seated position and above all to support his head.

Figure 2. Facial dysmorphias.



Wide forehead with prominent glabella, bilateral epicanthus, telecanthus, flattened nasal bridge, broad nasal base, anteverted nostrils, philtrum with accentuated pillars, dysmorphic retroposed auricles, low implantation, half-open mouth, micrognathia, among others.

Figure 3. Electroencephalography (EEG).



V-EEG in wakefulness and abnormal sleep due to altered brain maturation development and potentially fronto-central epileptiform activity.

Pathological Personal History

Patient under follow-up for recurrent respiratory infections that have merited multiple hospitalizations, currently under treatment with Fluticasone 125 mcg.Treated by gastroenterology for chronic constipation and dysphagia, medicated with Lactulosa.Hematology provides follow-up for hypochromic microcytic anemia.

In nutritional support due to moderate protein-caloric malnutrition, treated with elemental Zinc, multivitamin complex (Dayamineral (R)) and at 16m a gastric button is placed when presenting choking events when he eats and ingests liquids. Medicated by neurology with valproic acid when presenting seizures and an abnormal electroencephalogram (EEG) (see Figure 3).He receives physical therapy twice a week.

Cabinet tests

* Cranial CT: bifrontal cortical atrophy, unusual for the patient's age (see Figure 4).
* CT of paranasal sinuses: thickening of the bilateral osteomeatal complex.
* Abdominal USG: no pathological findings.
* Tympanometry, EOA, and evoked potentials: within normal parameters in both ears.
* Esophagus-stomach-duodenum series: no evidence of pathology.
* Ocular electrophysiology: response of the visual cortex to the light stimulus diminished.
* Ophthalmologic evaluation: myopia and oblique hyperfunction (TX. Optical correction).
* VEEG: during sleep there is frequent slow activity focused in bilateral pa-rasagittal region with predominance in fronto-central region followed by infrequent voltage attenuation.
* Karyotype: 46, XY.
* Echocardiogram: study within normal limits.
* TSH: 1.49 uIU/ml (VR 0.34- 5.60).
* T4: 0.40 ng/dl (VR 0.61- 1.12)
* T3: 3.24 ng/ml (VR 0.87- 1.78).

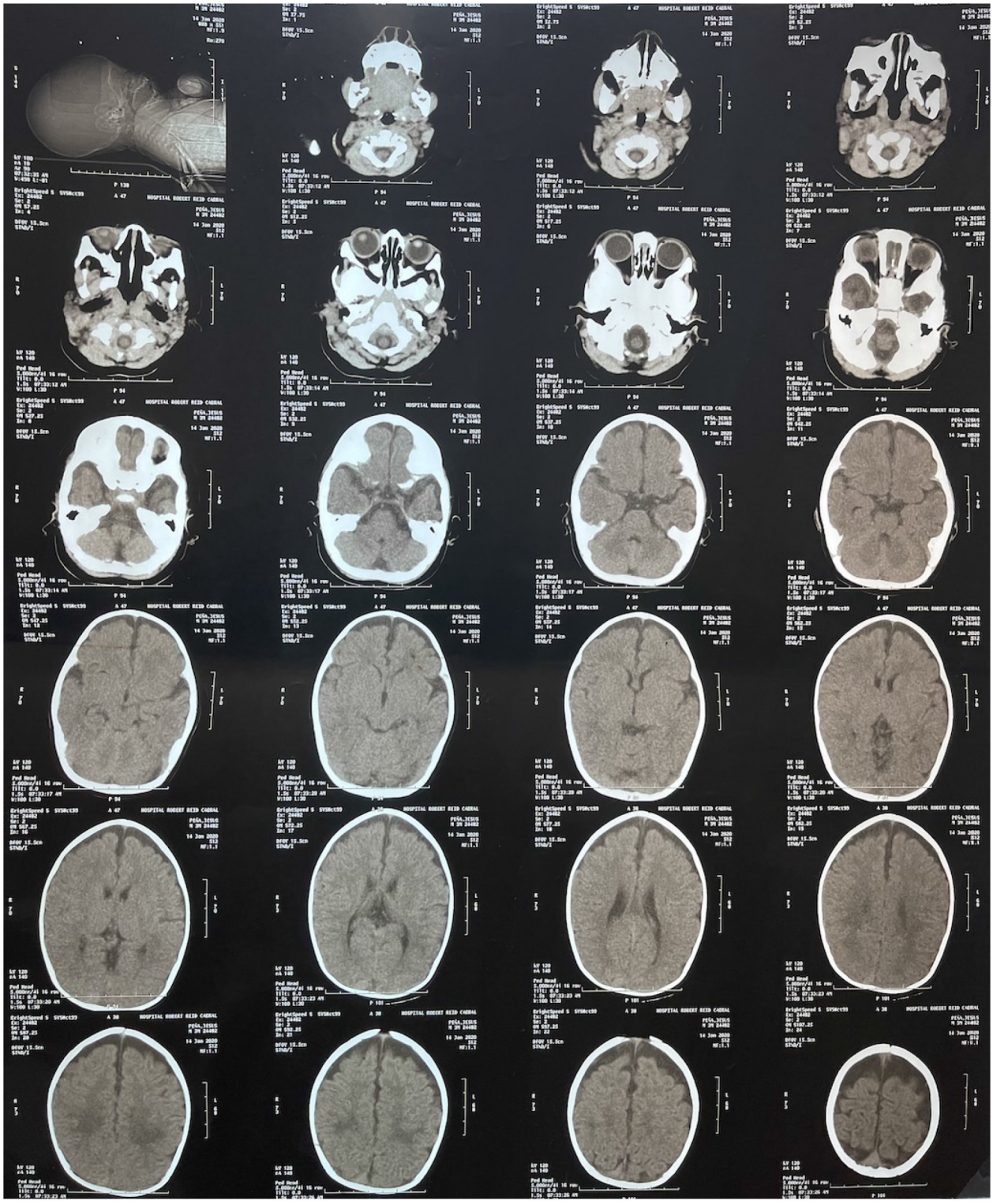
Anthropometric Measurements

Weight: 27 lb / 12.5 kg (3 percentile)

Height: 95 cm (3 percentile)

Height: 47 cm (5 percentile)

Figure 4. CAT scan of skull.



Bifrontal cortical atrophy, bifrontal subarachnoid space widening and deepening of the sulci and fissures of Sylvius.

Positive findings on physical examination

Patient with severe hypotonia, eupneic, hydrated, a phenotype consistent with: brachycephaly, broad forehead, prominent glabella, bilateral epicantus, telecanthus, flattened nasal bridge, broad nasal base, anteverted nares, philtrum with accentuated pillars, dysmorphic pinnae in retro position, low set, mouth with tendency to protrusion of the tongue, ajar, micrognathia, occasional chin movements, elongated neck, no cephalic support, symmetrical thorax, heart rhythmic heart sounds, no audible murmur, ventilated lungs, no rales, flaccid abdomen, diastasis of the rectus abdominis, no visceromegaly, phenotypically male genitalia, descended testicles, mobile extremities, symmetrical, with clinodactyly of the 5th finger of the hands, separation between the first and second metartarso bilateral (Sign of the san-dalia), joint hyperlaxity, decreased passive muscle tone, frog position, significant axial hypoto-nia, osteotendinous reflexes (bicipital, triceps, patellar, Achilles) ++/+ +++, dorsolumbar spine deviation, low weight, short stature, poor muscle tissue.

Whole exome sequencing was performed and reported positive (+):

A pathogenic copy number loss was identified in exon 1 of the *SLC16A2* gene. The result is consistent with the genetic diagnosis of Allan-Herndon-Dudley syndrome of X-linked inheritance (Hemizygous deletion: chrX:73641473-73641902).

According to HGMD Professional 20203, loss-of-function variants in this gene are disease-causing for Allan-Herndon-Dudley syndrome (PMID: 25517855, 15488219).

The generated library is sequenced on an Illumina platform to a read depth of at least 20x for 98% of the target bases. A proprietary bioinformatics approach is then applied, including alignment of the reads with the GRCh37/hg19 reference version of the human genome, variant annotation and filtering. All variants with minimum allele frequency (MAF) less than 1% in gnomAD as well as pathogenic variants reported in (ClinVar ID: 1077180) are considered for medical evaluation.

We found no evidence in DECIPHER that deletions in this gene are present in the healthy population. Therefore, the identified copy number variant was classified as pathogenic (class 1) following ACMG recommendations. Other candidate variants associated with severe hypotonia, neuromuscular disease, myopathies and severe early-onset pathologies compatible with the patient's phenotype were sought but no class 1 or 2 genes were detected.

Parental carrier testing was performed on the mother to determine whether the variant detected in the SLC16A2 gene is inherited or de novo. Paternal sequencing was not necessary since the inheritance pattern of this condition is X-linked.

In the mother an analysis of deletions/duplications in the *SLC16A2* gene confirmed the carrier status of the identified pathogenic variant: loss of a pathogenic copy of exon 1 of the *SLC16A2* gene in heterozygosis.

DISCUSSION

Genetic confirmation of the diagnosis provides a clear pathway for the clinical management of this disease and allows ruling out other possible conditions that equally cause severe hypotonia and intellectual disability. This is especially true in severe cases such as the one presented here because early and accurate diagnosis allows for optimized management, genetic counseling and treatment. Schwartz et al. (2005) had already underlined the clinical heterogeneity that can exist between different patients with SAHD and the importance of genetic diagnosis in these cases.

The clinical management of patients with SAHD is a significant challenge because of the multiple comorbidities that can accompany this pathology. Secondary complications, such as recurrent respiratory infections, anemia and malnutrition that this patient presented have been described (Groeneweg et al., 2019), emphasizing the need for a multidisciplinary clinical approach that includes the participation of specialties such as pediatrics, neurology, gastroenterology, pneumology, nutrition and physiotherapy, as occurred in our case (see Figure 5).

Monitoring should be strict and periodicity may vary depending on the severity and complexity of the case. In the case of a stable patient, it is recommended every 6 months until 4 years of age, followed by an annual follow-up, where developmental progress, neurological manifestations, constitutional,

musculoskeletal, gastrointestinal/feeding, pulmonary, thyroid, family support, among others, are assessed.It is important to consider emerging therapies. The use of triiodothyronine analog in the treatment of SAHD has been explored, although studies are still preliminary and definitive treatment has not been established [3].Although the penetrance and severity of this syndrome may vary, in this case a severe picture has manifested where profound intellectual disability was observed, accompanied by gait disability, aphasia and truncal hypotonia. In other cases, the consequences are earlier, which may include premature death or complications that accompany this syndrome. Complications usually occur secondary to recurrent infections and/or aspiration pneumonia. Given the patient's risk of bronchoaspiration, a gastric button was placed to minimize the risks. The differential diagnosis includes in very broad terms many disorders associated with hypotonia, ataxia, spastic paraparesis, seizures, muscular hypoplasia, severe intellectual disability with an autosomal recessive or X-linked inheritance pattern such as hypomyelinating leukodystrophies or early dystonia, being the main differential diagnoses: Pelizaeus-Merzbacher type disease due to mutations in the *GJC2 and PLP1* genes, *MECP2* duplication syndrome, as well as congenital non-goiter 6 hypothyroidism due to mutation in the *TRAS* gene.

Mutations in the monocarboxylate transporter 8 (*MCT8, SLC16A2*) gene, located on the X chromosome, cause severe psychomotor retardation syndrome and unusual thyroid function tests in males.

A study revealed as a major finding that the passage of the thyroid hormone analog (DITPA) crosses the placenta in mice. In addition, prenatal exposure to DITPA was found to have a significant effect on serum thyroid-stimulating hormone (TSH) levels and on the expression of thyroid hormone-dependent genes in the cerebral cortex of embryos. This finding could have implications for the development of the disease and the risk of transmission to future offspring [4].

CONCLUSION

Given the fact that Allan-Herndon-Dudley syndrome is underdiagnosed, its prevalence is still unknown. Our study supports the existing literature and suggests that it should be included in the differential diagnosis in all male patients with muscular hypotonia without a determined cause, as well as when we find in males altered thyroid hormone levels (e.g. abnormally elevated T3 levels, low to normal T4 levels, and normal to slightly elevated TSH levels).

Recalling that what would confirm the diagnosis would be molecular testing in which a variant would be determined which can be truncal, deletion, nonsense and missense variant in the *SLC16A2* gene (Xq13.2), which codes for monocarboxylate transporter 8 (MCT8), a specific transporter of thyroid hormone T3, the probable responsible for the neurological problems due to the inability to trans-port thyroid hormone T3 into some neuronal cells.

More effective therapies, possibly along the lines of tri-iodothyronine analogs, should be considered to address neuromuscular symptoms in severe cases. The variability in symptom presentation, even within the same family (as indicated by the asymptomatic carrier mother), is an area requiring further investigation. This case adds the importance of early detection and multidisciplinary management to improve the quality of life of patients and their families.

Author Contributions

Bary G. Bigay Mercedes, MD. MSC. Clinical & Molecular Medical Geneticist, Director of the ChromoMED Institute.

Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this case report.

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