CASO CLÍNICO/CASE REPORT

Global Hypotonia, Areflexia and Severe Cognitive Impairment: A *TECPR2*-HSAN with Intellectual Disability Case Report

Hipotonia, Arreflexia e Défice Cognitivo: Um Caso de *TECPR2*-HSAN com Défice Intelectual

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Abstract

TECPR2-related hereditary sensory and autonomic neuropathy with intellectual disability (*TECPR2*-HSAN with ID) is a rare and complex neurological disorder characterized by developmental delay, hypotonia, intellectual disability, ataxia, paraplegia and areflexia. Most patients experience autonomic dysfunction, central hypoventilation, and die before the third decade of life.

We report the case of a seven-year-old boy with dysmorphic features, axial hypotonia from birth, and global developmental delay progressing to lower-limb areflexia, severe intellectual disability, dysarthria and ataxia. He experienced nocturnal apneas and episodes of dysphagia and choking, some associated with aspiration pneumonia and decreased alertness. Extensive investigations were inconclusive until exome sequencing at age 16 identified a homozygous variant in the *TECPR2* gene, confirming the diagnosis.

This case contributes to the limited literature on this rare disorder and highlights its progressive multisystem involvement and diagnostic challenges. Early exome sequencing can reduce diagnostic delay, guiding management, anticipatory care, and family counseling.

Resumo

A neuropatia hereditária sensitivo-autonómica com défice intelectual associada ao gene *TECPR2* (*TECPR2*-HSAN com défice intelectual) é uma doença neurológica complexa e rara caracterizada por atraso do desenvolvimento, hipotonia, défice intelectual, ataxia, paraplegia e arreflexia. A maioria dos doentes apresenta disfunção autonómica, hipoventilação central, e morre antes da terceira década de vida.

Descrevemos o caso de um rapaz de sete anos, com dismorfias faciais, hipotonia axial desde o nascimento e atraso global do desenvolvimento, que evoluiu para arreflexia dos membros inferiores, défice intelectual grave, disartria e ataxia. Apresentou apneias noturnas e episódios de disfagia e engasgamento, alguns com pneumonia de aspiração e diminuição do estado de consciência. Extensa investigação foi inconclusiva até que, aos 16 anos, a sequenciação de exoma identificou uma variante homozigótica no gene *TECPR2*, confirmando o diagnóstico.

Este caso contribui para a escassa literatura existente sobre esta doença rara, realçando o envolvimento multissistémico progressivo e desafio diagnóstico. A sequenciação de exoma precoce pode reduzir o atraso diagnóstico, e orientar a abordagem clínica, aconselhamento familiar e cuidados antecipatórios.

Introduction

In 2012, Oz-Levi *et al* described a distinctive spectrum of symptoms in five members of three independent Jewish Bukharian families, all of whom carried a homozygous pathogenic variant in the *TECPR2* (tectonin beta-propeller repeat containing 2) gene. The affected individuals displayed spastic paraparesis, areflexia, and intellectual disability, and the authors considered this condition a novel form of complicated hereditary spastic paraplegia (SPG49).[1]

In 2016, Heimer *et al* reported three additional patients with biallelic *TECPR2* pathogenic variants. They observed that, in addition to the symptoms previously described, the syndrome's primary disabling feature was a sensory and autonomic neuropathy. Consequently, the disease was reclassified as hereditary sensory and autonomic neuropathy type IX with developmental delay (HSAN9) and named *TECPR2*-related hereditary sensory and autonomic neuropathy with intellectual disability.[2,3]

TECPR2-HSAN with ID is an extremely rare disease, with only five publications and 27 cases reported in the literature.[1,3-6] It follows an autosomal recessive inheritance pattern and parental consanguinity and Bukharian or Ashkenazi Jewish ancestry are risk factors.[3,4,7]

It is characterized by developmental delay and subsequent moderate to severe intellectual disability. Global hypotonia usually presents within the first two years of life, and progresses to spastic paraplegia over time. Gait is often ataxic, and patients develop a small fiber sensory neuropathy, presenting as lower-limb hypo- or areflexia and reduced pain sensitivity. Dysarthria is common and individuals may be nonverbal.[1,3,4,7,8]

Autonomic dysfunction is another key feature, often manifesting as gastrointestinal dysmotility, constipation and gastroesophageal reflux disease (GERD). GERD and dysphagia can lead to aspiration and recurrent respiratory infections, which may cause severe lung disease. Brainstem dysfunction with central hypoventilation and apnea are also common, initially occurring during sleep and later during wakefulness, often requiring ventilatory support.[7,8]

Affected individuals may have dysmorphic features such as short stature, chubby appearance, microcephaly, brachycephaly, low anterior hairline and coarse facial features including synophrys, thick eyebrows, hypotelorism and dental crowding.[2,7,8] Epilepsy and abnormal epileptiform EEGs are infrequent, while behavioral abnormalities like hyperactivity are common.[3,4,7]

Life expectancy is reduced, with all reported patients dying in the first two decades of life, primarily due to asphyxia related to food aspiration, central apnea, or complications of chronic progressive lung disease.[3,4,7]

The diagnosis can be established when there are suggestive clinical findings and biallelic pathogenic (or likely pathogenic) variants in the *TECPR2* gene identified by molecular genetic testing. There are no disease-modifying treatments, and supportive care is recommended to improve quality of life, enhance function and reduce complications.[7]

Case Report

A 7-year-old boy, born to healthy consanguineous parents, presented to the Neuropediatrics outpatient department with axial hypotonia from birth and global developmental delay. There was no family history of neurological disorders.

Prenatal ultrasound at 29 weeks of gestation revealed isolated dilation of the posterior horn of the right lateral ventricle. The fetal karyotype was normal. The child was born at term via elective cesarean section after an otherwise uneventful pregnancy, with a birth weight of 2615 g (small for gestational age) and an Apgar score of 9/10. He was admitted to the Neonatal Care Unit due to hypotonia, and cranial ultrasound and later magnetic resonance imaging (MRI), showed bilateral colpocephaly (**Fig. 1**).

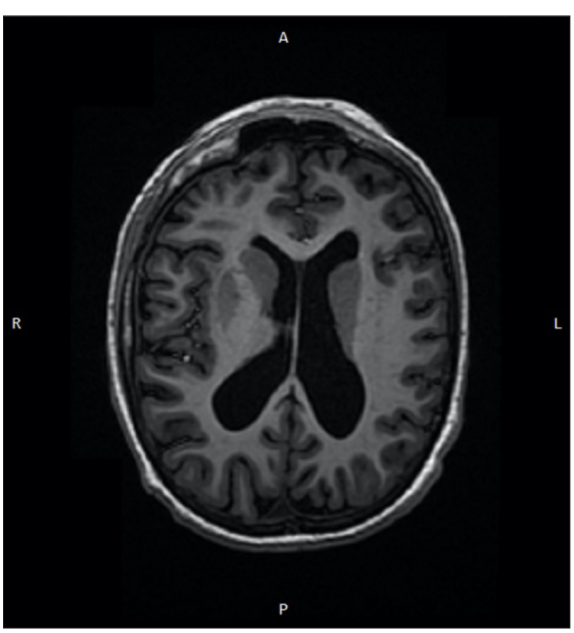

Figure 1. T1-weighted axial MRI section of the patient's brain at age 13, showing bilateral colpocephaly.

During the first two years of life, he experienced several respiratory infections, some requiring hospitalization, and was diagnosed with recurrent wheezing and asthma.

He started walking with support at 18 months and independently, though with a clumsy gait, at 21 months. He spoke his first words at age two. Daytime bladder and bowel control were achieved at age three, but nocturnal enuresis persisted.

Physical examination at age seven revealed truncal obesity, coarse facial features, and ligamentous laxity (**Fig. 2.A**). Neurological examination showed dysarthria, global hypotonia, hyporeflexia of the upper and areflexia of the lower limbs, and ataxic gait. The child was normocephalic, and stature was between the 3rd and 15th percentiles.

The condition progressed with severe intellectual disability and marked dysarthria. He had chronic constipation and never experienced seizures. Clinical examination at age 11 showed additional dysmorphic features, such as triangular face, ogival palate, bilateral ptosis, hypomimia, scoliosis, and *genu flexum*. Apart from astigmatism and bilateral ptosis, he exhibited no other ophthalmological findings.

During adolescence the patient developed severe sleep apnea and recurrent episodes of dysphagia with choking and aspiration pneumonia. During some episodes of respiratory distress, he had periods of decreased alertness, sometimes lasting hours. He was hospitalized and required treatment with broad-spectrum antibiotics on numerous occasions, and underwent invasive mechanical ventilation and intensive care unit admission twice. Videofluoroscopic swallow study revealed oropharyngeal dysphagia, worse with solid foods.

Speech became unintelligible, ataxia aggravated and reflexes were absent. He exhibited increasingly frequent bursts of agitation and aggressive behavior that motivated treatment with neuroleptics, with limited benefit. **Fig. 2.B** illustrates the patient's phenotype at age 15.

Throughout his life, he underwent broad and thorough investigations, including karyotype, genetic testing for Prader-Willi syndrome, electromyography, muscle biopsy, somatosensory evoked potentials, upper gastrointestinal endoscopy, sleep and awake EEG, and molecular testing for fragile X syndrome and subtelomeric rearrangements, which were overall non-contributory.

Exome sequencing at age 16 identified the variant of unknown significance c.877T>C in the *TECPR2* gene (NM_014844.4), in apparent homozygosity (confirmed in a subsequent study of his parents). Although this variant had not been previously documented, it explained the phenotype and supported the diagnosis of *TECPR2*-HSAN with ID.

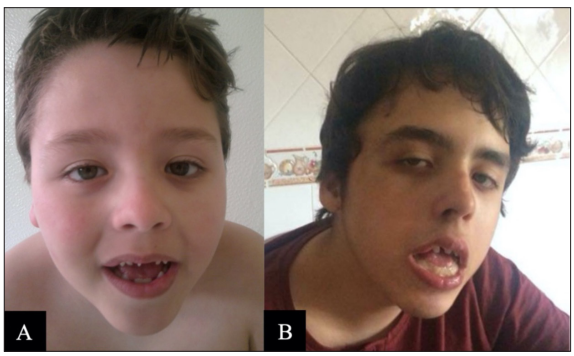

Figure 2. Patient's facial phenotype at 7 (A) and 15 years old (B). At 7yo the patient exhibited a chubby appearance, prominent forehead, low-set ears, long philtrum, dental crowding and a short neck. At 15yo the patient showed bilateral ptosis, hypomimia and a dropped jaw.

He passed away at age 17 due to respiratory insufficiency following a severe pulmonary infection.

Discussion

Impairment in autophagy, a process by which cells remove dysfunctional organelles or misfolded proteins, is especially relevant for neurons and has been identified in lysosomal storage diseases, Huntington's disease, and amyotrophic lateral sclerosis. *TECPR2* protein's involvement in autophagy has been well documented and its knockout resulted in progressive degeneration of the brain, brainstem and peripheral nervous system.[3,7,9,10]

We describe the phenotypic features and clinical evolution of a patient with *TECPR2*-HSAN with ID, an exceptionally rare disease only recently described and classified.

Dysmorphic facial features have been noted, as in our case, although not with an easily recognizable facial gestalt.[3-5]

Similar to other reported cases, our patient had early hypotonia and developmental delay, which progressed to severe intellectual disability, ataxia, areflexia, and anarthria. Unlike our patient, others lost the ability to walk, and many patients also developed hyperactivity and bursts of aggressive behavior.[4,7]

One cardinal feature of *TECPR2*-HSAN with ID is disturbed breathing, apnea, and recurrent episodes of as-

piration. Chronic lung disease and/or respiratory insufficiency may require nighttime ventilation, tracheostomy and even chronic mechanical ventilation.[1,3-5] It seems to be among the genetic disorders characterized by abnormal brainstem regulation of breathing, such as Rett, Joubert, ROHHAD syndromes, and Ondine's curse.[6]

On MRI, several abnormal findings have been reported, including thin corpus callosum, ventricular enlargement, and colpocephaly (the latter seen in our case).[4,7]

As this is a small fiber neuropathy, motor and sensory nerve conduction are normal, while areflexia and pain insensitivity are often present.[7,11] Self-mutilation occurs in some HSANs with congenital insensitivity to pain, and even though recognizing insensitivity to pain in a nonverbal child with abnormal behavior may be challenging, this has not been reported in *TECPR2*-HSAN with ID and was also absent in our case. Severe GERD and constipation may be due to parasympathetic denervation, and we speculate that ptosis may result from sympathetic dysautonomia.[12]

This peculiar clinical presentation leads to a broad differential diagnosis that may considerably delay diagnosis. Parental consanguinity may suggest recessive inheritance, but family history may not be present. In our case, there was a considerable delay in appropriate genetic workup since exome sequencing was not readily available at the time.

Therefore, when approaching a patient with such similarly multi-faceted neurological presentation, exome sequencing should be considered early in the diagnostic process. Accurate disease identification is crucial for the patient and their family, as it enables genetic and reproductive counseling, while guiding clinicians in effective disease management and prognosis. ■

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Contributorship Statement / Declaração de Contribuição

MIN, MM: Research, conception of the work, drafting of the manuscript.

IB, MA: Clinical evaluation of the patient, revision of the manuscript.

JPV, SR: Research, conceptionof the work, clinical evaluation of the patient, revision of the manuscript, supervision of the work.

All authors approved the final version to be published.

MIN, MM: Pesquisa e conceção do trabalho, redação do manuscrito.

IB, MA: Avaliação clínica do doente, revisão do manuscrito.

JPV, SR: Pesquisa e conceção do trabalho, avaliação clínica do doente, revisão do manuscrito, supervisão do trabalho.

Todos os autores aprovaram a versão final a ser publicada.

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