CASO CLÍNICO/CASE REPORT

Infantile Neuroaxonal Dystrophy: Clinical Case

Distrofia Neuroaxonal Infantil: Caso Clínico

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DOI: https://doi.org/10.46531/sinapse/CC/149/2025

Informações/Informations:
Caso Clínico, publicado em Sinapse, Volume 25, Número 4, outubro-dezembro 2025. Versão eletrónica em www.sinapse.pt; Case Report, published in Sinapse, Volume 25, Number 4, October-December 2025. Electronic version in www.sinapse.pt

Keywords:
Child;
Neuroaxonal Dystrophies/genetics;
Neurodegenerative Diseases/genetics.

Palavras-chave:
Criança;
Distrofias Neuroaxonais/genética;
Doenças Neurodegenerativas/genética.

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Recebido / Received: *2025-03-12*
Aceite / Accepted: *2025-11-19*
Publicado / Published: *2025-12-31*

Abstract

Infantile neuroaxonal dystrophy is a rare neurodegenerative disorder caused by mutations in the *PLA2G6* gene and is part of the neurodegeneration with brain iron accumulation disease group. We present the case of a three-year-old male with a six-month history of neurodevelopmental regression, including motor and speech regression. Brain magnetic resonance imaging (MRI) revealed characteristic findings such as claval hypertrophy and symmetrical cerebellar atrophy, prompting targeted genetic testing which confirmed a compound heterozygous mutation in the *PLA2G6* gene. This case emphasizes the importance of integrating clinical, imaging, and genetic findings for the early diagnosis of infantile neuroaxonal dystrophy, highlighting the critical role of pathognomonic MRI features.

Resumo

A distrofia neuroaxonal infantil é uma doença neurodegenerativa rara causada por mutações no gene *PLA2G6* e integra o grupo de doenças neurodegenerativas por acumulação de ferro. Apresentamos o caso de uma criança de três anos de idade do sexo masculino com história de regressão do neurodesenvolvimento com seis meses de evolução, incluindo regressão motora e da linguagem. A ressonância magnética cerebral revelou achados característicos, como hipertrofia claval e atrofia cerebelar simétrica, que motivaram a realização de testes genéticos dirigidos que confirmaram uma mutação heterozigótica composta do gene *PLA2G6*. Este caso destaca a importância da integração clínica, imagiológica e genética para o diagnóstico precoce de distrofia neuroaxonal infantil, destacando o papel fulcral dos achados patognomónicos da ressonância magnética cerebral.

Introduction

Infantile neuroaxonal dystrophy (INAD) is a devastating autosomal recessive neurological disorder with an estimated prevalence of 1 in 1 000 000 individuals.[1] It stands as a prominent subtype of PLA2G6-associated neurodegeneration (PLAN), a group of rare neurodegenerative disorders caused by biallelic loss-of-function mutations in the *PLA2G6* gene. This gene encodes group VI calcium-independent phospholipase A2, a crucial enzyme for lipid metabolism and membrane stability.[2] While clinical and imaging features often overlap, three primary phenotypes have been distinguished based on age of onset and disease progression: INAD, atypical late-onset neuroaxonal dystrophy, and PLA2G6-related dystonia-parkinsonism.[3] PLAN also falls under the broader category of neurodegeneration with brain iron accumulation (NBIA) disorders.[1]

Although PLAN disorders exhibit variable clinical presentations, INAD is characterized by early onset, typically within the first two to three years of life, with rapid progression.[1,2] Initial symptoms encompass developmental delay or regression, such as loss of head control, impaired ability to sit, crawl, walk, or speak, alongside truncal hypotonia, strabismus, and nystagmus.[3] Moreover, over one in five patients may manifest facial dysmorphism, including a prominent forehead, frontal bossing, and a depressed nasal bridge. Seizures may manifest at any disease stage, despite being reported in a minority of patients.[2] Over time, patients develop spastic tetraparesis, optic atrophy, and severe cognitive decline, often succumbing to the disease within the first decade.[4,5] The rarity of the condition and its symptom overlap with other disorders complicate diagnosis, with genetic testing serving as the gold standard. However, approximately 15% of patients with an INAD phenotype lack identifiable *PLA2G6* mutations, underscoring genetic heterogeneity.[6] Neuroimaging plays a pivotal role in diagnosis. Brain magnetic resonance imaging (MRI) findings, such as symmetrical cerebellar atrophy, claval hypertrophy, and abnormal iron deposition in the basal ganglia (with signal loss in the *globus pallidus*), are crucial in distinguishing INAD from other neurodegenerative conditions.[2,7]

Despite advances in diagnostic techniques, therapeutic options remain limited. Current management focuses on symptom relief and quality of life improvement through a multidisciplinary approach, including early intervention, physical therapy, nutritional support, and anticonvulsants. However, experimental treatments, such as gene therapy and enzyme replacement, are actively under investigation.[1,8]

Early recognition and comprehensive care are imperative to mitigate the impact on children with INAD and their families. A coordinated team of healthcare professionals, encompassing pediatric neurologists, physical and occupational therapists, speech therapists, pediatricians, and social workers, is essential to address the holistic needs of these patients.

Case Report

We present the case of a firstborn child of a young, healthy, non-consanguineous couple with no notable familial background. The child was delivered vaginally at 40 weeks of gestation after an uncomplicated, closely monitored pregnancy. He demonstrated normal growth patterns in terms of length and weight, with no signs of restricted dietary intake or dysphagia. The child achieved significant developmental milestones, such as sitting independently and crawling at eight months, standing at twelve months, and walking at eighteen months. Noteworthy medical history included an evaluation at six months for a sacrococcygeal dimple, with an MRI of the spine revealing no underlying abnormalities, and an ophthalmic examination one week prior to the pediatric visit ruling out strabismus.

At three years of age, the patient presented with a six-month history of progressive motor regression, such as the loss of independent walking and frequent falls, as well as speech regression, marked by a limited vocabulary and difficulty forming full sentences.

There was no documented history of trauma or fever. Although his social interaction was good, his lexicon was limited hindering his ability to construct complete sentences.

Clinical examination revealed no major dysmorphisms. The patient demonstrated proficient head and truncal control while seated. He exhibited isocoric and isoreactive pupils, alongside a noticeable right convergent strabismus, without opthalmoparesis or nystagmus. Facial expressions and tongue movements were symmetrical, with a present gag reflex. Muscle strength remained intact, with absence of upper limb spasticity. However lower limb spasticity and hyperreflexia, including a positive Babinski reflex, were evident. Sensory

functions displayed no abnormalities. An unsteady gait characterized by tiptoeing and a broad-based stance was observed, with an apparent risk of falling without support. The patient exhibited difficulty rising from the floor. Additional observations included valgus deformity of the knees with hyperextension, hip flexion, and valgus positioning of the feet.

Electromyography, electroencephalography and a head computed tomography scan revealed no abnormalities. Blood tests were largely unremarkable, except for mildly elevated aspartate aminotransferase (AST) at 53 U/L, erythrocyte sedimentation rate at 44 mm, and ammonia at 43 μmol/L. Alanine aminotransferase (ALT) was normal, with an elevated AST/ALT ratio of 2.94. Additionally, there were slight elevations in lactate levels and the lactate/pyruvate ratio. The metabolic disease panel returned negative results, and a nerve biopsy was not performed.

Brain MRI revealed cerebellar atrophy, abnormal signal intensity in the *globus pallidus* and claval hypertrophy (**Fig. 1**), prompting targeted genetic testing for *PLA2G6* gene mutations. Genetic analysis confirmed a compound missense heterozygous mutation, with allele variants c.2032A>G (p.Lys678Glu) and c.2370T>G (p.Tyr790*), classified as likely pathogenic and pathogenic, respectively, following parental testing. A diagnosis of INAD was confirmed, and the patient was offered supportive therapy, including physiotherapy, speech therapy, early intervention, and genetic counseling.

During follow-up, the disease progressed with the onset of axial hypotonia, as well as hypertonia and hyperreflexia in the lower limbs, along with the loss of independent walking ability within one year after diagnosis, resulting in wheelchair use by age four despite physiotherapy support. A slight improvement in speech was noted, with the child able to form two- to three-word sentences. At the last appointment, by the age of five years and 10 months, the child had lost the ability to sit without support and exhibited sialorrhea, sphincter incontinence, and dysphagia, with occasional choking during meals. There was no history of seizures. On examination, the child demonstrated spastic tetraparesis but retained some ability to interact and vocalize.

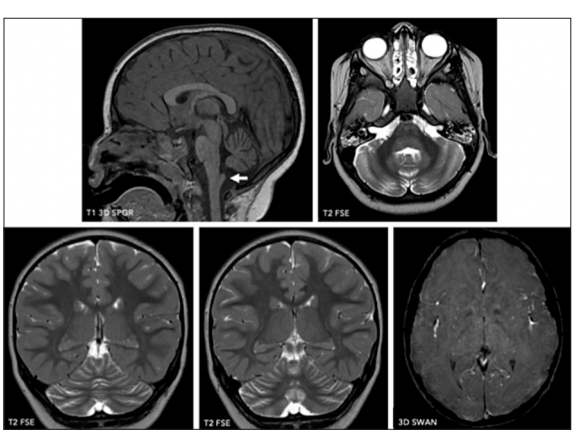

Figure 1. Brain MRI showed symmetrical cerebellar atrophy, signal loss in the *globus pallidus* on susceptibility-weighted imaging, and claval hypertrophy [arrow], suggesting the diagnosis of PLAN/INAD in conjunction with the clinical features.

Discussion

The clinical presentation of this patient aligns closely with the characteristic features of INAD, as described in literature. The initial symptoms of neurodevelopmental regression, particularly the gradual loss of motor skills, were among the earliest signs of disease progression.

Neurological examination revealed pyramidal (tiptoe gait, lower-limb spasticity, hyperreflexia, and Babinski sign) and cerebellar involvement (broad-based stance, with difficulty standing without support).

The gradual onset of these early motor deficits, along with their overlap with multiple differential diagnoses, highlights the challenges in identifying INAD during its early stages.

Upon clinical examination, several hallmark signs of INAD were noted. Research shows that approximately 68% of patients with INAD experience developmental delays, with delayed speech occurring in nearly 90% of these, before the onset of more severe symptoms. Tiptoe gait, often linked to increased tension in the *triceps surae*, is observed in over half of affected individuals. Additionally, about 80% of patients with INAD present with spastic hypertonia.[2,8] These findings, combined with the patient's developmental regression, point to the neurodegenerative nature of the disorder.

An international study reported that 91% of tested INAD patients exhibited elevated AST, often accompanied by an increased AST/ALT ratio,[2,10] suggesting underlying mitochondrial dysfunction. In our case, a mild AST elevation and high AST/ALT ratio were present,[2,9,10] supporting the potential role of these parameters as diagnostic biomarkers. However, further research is needed to clarify their diagnostic and prognostic value.[10]

Despite the absence of any abnormal findings in the initial metabolic evaluation, the exclusion of strabismus

through ophthalmologic assessment, and the lack of evident craniofacial dysmorphisms, the constellation of clinical manifestations suggestive of a neurodegenerative condition justified the pursuit of further diagnostic assessments.

MRI features such as symmetrical cerebellar atrophy, claval hypertrophy, and signal loss in the *globus pallidus* are hallmark findings in INAD, helping to differentiate it from other neurodegenerative conditions. These findings prompted focused genetic testing.

Genetic analysis confirmed a compound heterozygous mutation, with allele variants c.2032A>G (p.Lys678Glu) and c.2370T>G (p.Tyr790*), classified as likely pathogenic and pathogenic, respectively, confirming the diagnosis.

The rapid progression of symptoms, including loss of independent walking within one year and development of spastic tetraparesis, is consistent with the aggressive nature of INAD. The patient's functional decline, including sphincter incontinence and dysphagia, underscores the severe impact of this disorder on daily life. These symptoms illustrate the extensive motor and bulbar dysfunction characteristic of late-stage INAD.[2]

This case highlights the critical importance of early diagnosis of INAD through a combination of clinical evaluation, neuroimaging, and genetic testing.[8] Early diagnosis facilitates timely genetic counseling, management, and the provision of supportive therapies, involving a multidisciplinary pediatric palliative care team, ultimately improving the quality of life for affected children.

Given that INAD is a fatal and progressive disorder with limited therapeutic options, ongoing research into disease-modifying therapies remains imperative to address the unmet intricate needs of this devastating condition. Heightened awareness and interdisciplinary collaboration among clinicians are paramount to enable early diagnosis, optimize adjuvant treatment opportunities, and enhance the quality of life for children impacted by INAD. ■

Contributorship Statement / Declaração de Contribuição

FA and IN: Design, data acquisition, content review, and approval of the final version to be published.

CC, ALR, and EV: Content review and approval of the final version to be published.

FA e IN: Desenho, aquisição de dados, revisão de conteúdo e aprovação da versão final a ser publicada.

CC, ALR e EV: Revisão de conteúdo, aprovação da versão final a ser publicada.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

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