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# A Rare Leukodystrophy Revealed in a Moroccan Infant: A Case Report of Canavan Disease

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**Abstract** | **Case Report**

***Introduction:*** Canavan disease is a rare autosomal-recessive leukodystrophy characterized by spongiform degeneration of the cerebral white matter secondary to aspartoacylase (ASPA) deficiency. It presents early with axial hypotonia, global psychomotor delay, and progressive macrocephaly. ***Objective:*** This work aims to illustrate the clinical, biological, and radiological particularities of this disorder through a Moroccan case. ***Case Report:*** We report the case of a 10-month-old female infant, born to first-degree consanguineous parents, presenting with severe axial hypotonia, absence of head control, generalized seizures, and macrocephaly. Brain MRI showed diffuse, symmetrical T2-weighted hyperintensities of the white matter, typical of spongiform leukodystrophy. Urinary assay revealed marked elevation of N-acetyl-aspartic acid (NAA), and molecular analysis confirmed homozygosity for the c.924del ASPA mutation. Management was symptomatic, including motor rehabilitation and nutritional assistance. ***Discussion:*** This observation illustrates the severe infantile form of Canavan disease. The combination of macrocephaly, developmental delay, and diffuse white-matter abnormalities should alert the clinician. Although differential diagnoses include other leukodystrophies, increased NAA and molecular confirmation are specific. Familial consanguinity and the presence of an affected sibling highlight the need for family screening and genetic counseling. ***Conclusion:*** Although no curative treatment exists, early identification of this rare disease allows appropriate management and opens perspectives for innovative therapeutic strategies, particularly gene therapy.

**Keywords:** Canavan disease; Leukodystrophy; Macrocephaly; Psychomotor delay.



## INTRODUCTION

Canavan disease is a rare autosomal-recessive leukodystrophy first described by Canavan in 1931 [1] and later characterized by Van Bogaert and Bertrand in 1949 [2]. In 1988, Matalon *et al.,* identified an aspartoacylase (ASPA) deficiency caused by mutations in the ASPA gene on chromosome 17p [3]. ASPA hydrolyzes N-acetyl-L-aspartate (NAA) into aspartate and acetate; its absence leads to cerebral accumulation of NAA, causing osmotic imbalance and diffuse dysmyelination [4, 5].

Clinically, the infantile form predominates, featuring axial hypotonia, macrocephaly, psychomotor delay, spasticity, and sometimes seizures [6–8]. The evolution is usually unfavorable, although milder juvenile forms with slower progression have been reported [9, 10].

Diagnosis relies on clinical and radiological findings (diffuse white-matter involvement and NAA peak on MRS) [11, 12], together with marked NAA increase in biological fluids [13]. Molecular confirmation is achieved by ASPA gene sequencing.

Although no curative therapy exists, gene therapy and acetate precursors provide promising perspectives [14–16]. Here, we report a Moroccan case illustrating the clinical, biological, and radiological features of this disease.

The objective of this work is to describe a Moroccan case of Canavan disease, detailing its clinical, radiological, biochemical, and genetic characteristics. Through this observation, we aim to emphasize the importance of early diagnosis—particularly in consanguineous contexts—and to highlight recent

therapeutic advances, especially gene-therapy approaches.

## Case Report

M.A., a 10-month-old female infant, was admitted to the pediatric department for evaluation of a global psychomotor developmental delay and progressive macrocephaly. She was born to first-degree consanguineous parents. The family history revealed a brother who had died with a similar early-onset neurological disorder, reinforcing the hypothesis of an autosomal recessive inherited disease. The father, otherwise asymptomatic, was known to be a heterozygous carrier of an ASPA gene mutation. Pregnancy and delivery were uneventful, and birth weight was within normal limits.

From the first weeks of life, the parents noticed significant feeding difficulties due to weak and ineffective sucking, requiring frequent pauses during breastfeeding. Psychomotor development rapidly became concerning: absence of head control, inability to roll over, delayed sitting position, and absence of voluntary grasp. Additional signs included constant irritability, excessive sleepiness, and several generalized seizures beginning at six months of age, for which antiepileptic treatment was initiated. The parents also reported an absence of babbling and progressive loss of visual contact, suggesting impairment of cognitive and sensory functions.

On clinical examination, the child presented with macrocephaly, with a head circumference above the 97th percentile, contrasting with preserved weight and height growth. Muscle tone was profoundly altered: marked axial hypotonia associated with emerging peripheral hypertonia. Deep tendon reflexes were brisk and diffuse, indicating pyramidal involvement, and the Moro reflex persisted beyond the expected age. Neurological examination revealed absent visual tracking and suspected bilateral optic atrophy. Nutritional status remained relatively preserved, but the infant exhibited marked fatigability and a tendency to recurrent respiratory infections.

Brain MRI revealed diffuse and symmetrical white-matter abnormalities, showing T2-weighted hyperintensities predominant in the frontal and parietal subcortical regions, with relative preservation of the basal ganglia and cerebellum (Figure 1). These findings were consistent with spongiform leukodystrophy. Magnetic resonance spectroscopy was not performed, but the metabolic work-up revealed a marked elevation of urinary N-acetyl-aspartic acid (NAA), confirmed by gas chromatography–mass spectrometry (GC-MS).

Molecular analysis confirmed the diagnosis: the patient was homozygous for the c.924del ASPA gene mutation, previously reported in the literature as pathogenic for Canavan disease. The father was identified as a heterozygous carrier of the same mutation.

Management was based on symptomatic care. Early motor and psychomotor rehabilitation was initiated to prevent orthopedic complications due to hypotonia and secondary spasticity. Oral feeding became increasingly difficult because of dysphagia, leading to progressive implementation of nasogastric nutritional support. A multidisciplinary follow-up was provided, including pediatric neurology, physical therapy, ophthalmology, and nutrition. Despite these measures, disease progression was marked by worsening developmental delay, regression of previously acquired milestones, and increased susceptibility to intercurrent infections. Long-term follow-up information for this patient was unavailable from the reference center.

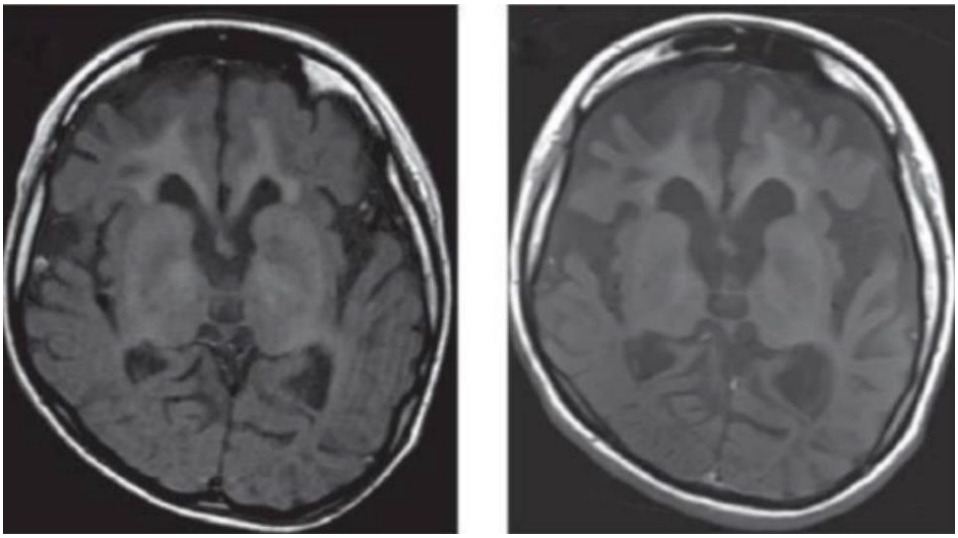

**Figure 1: Axial brain MRI slices in a patient with Canavan disease showing diffuse, symmetrical T2-weighted hyperintensities of the white matter, with relative preservation of the basal ganglia**

## DISCUSSION

Canavan disease is a rare hereditary leukodystrophy with autosomal recessive transmission, first described in 1931 by Myrtelle Canavan based on histopathological findings from the brain of a deceased child [1]. It is characterized by diffuse spongiform degeneration of the cerebral white matter associated with pathological accumulation of N-acetyl-aspartic acid (NAA). This metabolic abnormality results from a deficiency of aspartoacylase (ASPA), an enzyme localized in oligodendrocytes and encoded by the ASPA gene on chromosome 17p13-ter [2]. The absence of enzymatic activity blocks the hydrolysis of NAA into aspartate and acetate, the latter being an essential substrate for myelin lipid synthesis. The lack of myelination and the osmotically active accumulation of NAA lead to intramyelinic edema responsible for the typical spongiform vacuolation observed on neuropathological examination [3,4].

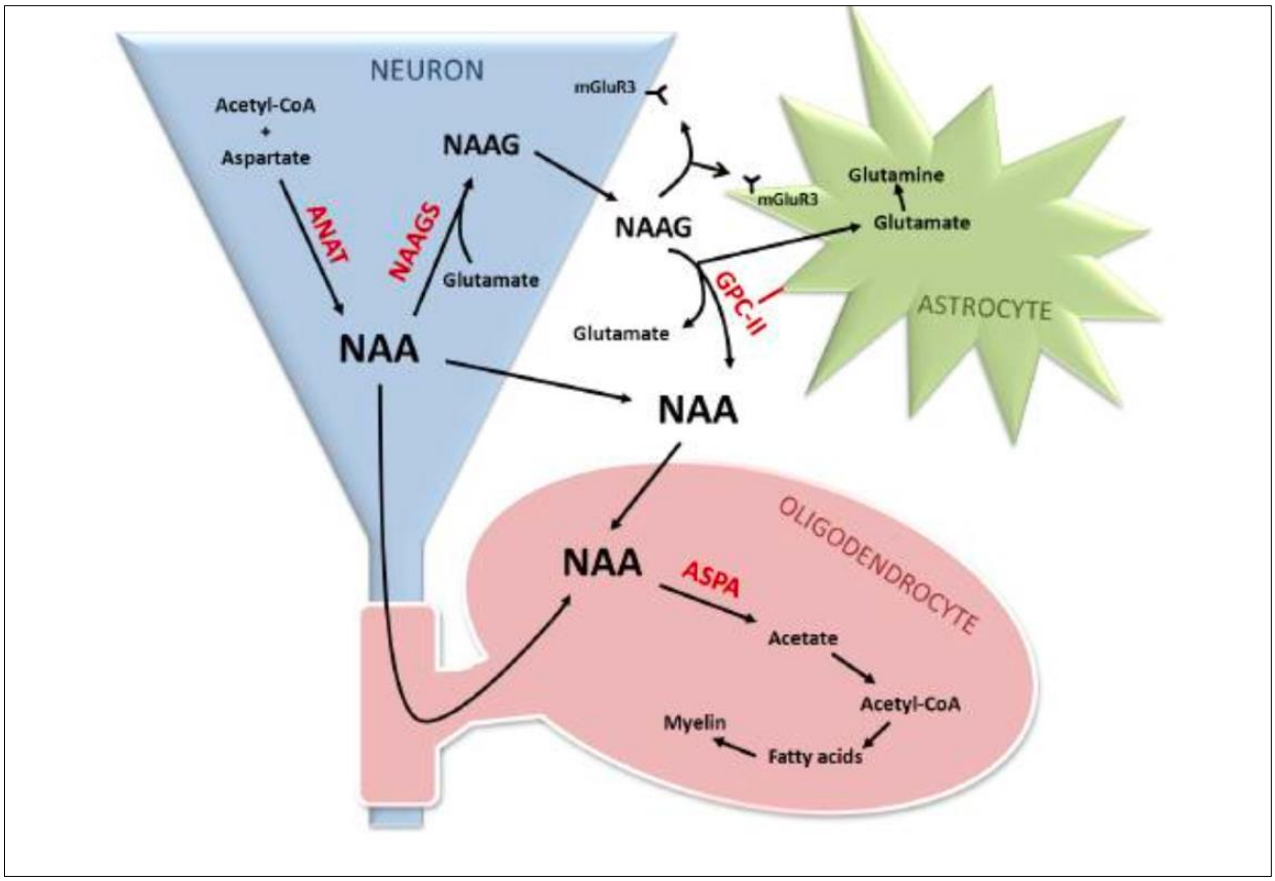


**Figure 2: Diagram of N-acetyl-aspartate (NAA) metabolism and its interactions between neurons, oligodendrocytes, and astrocytes**

NAA is synthesized in neurons from acetyl-CoA and aspartate by acetyl-CoA/aspartate N-acetyltransferase (ANAT), and may then be converted into N-acetyl-aspartylglutamate (NAAG) via NAAG synthase (NAAGS). NAAG released into the extracellular space is hydrolyzed by astrocytic glutamate carboxypeptidase II (GPC-II), releasing glutamate, which is converted to glutamine for neuronal recycling. NAA itself is taken up by oligodendrocytes, where it is hydrolyzed by aspartoacylase (ASPA) into acetate and aspartate; acetate contributes to myelin lipid synthesis, illustrating the crucial role of the NAA system in neuron–glia metabolic communication.

NAA is an abundant metabolite in the central nervous system, synthesized almost exclusively by neurons. Its physiological role remains partially unclear, but it appears to be involved in osmotic homeostasis, acetate transport for lipid synthesis, and neuronal signaling [5]. Aspartoacylase is expressed in oligodendrocytes and catalyzes the hydrolysis of NAA. In Canavan disease, the absence of ASPA leads to accumulation of NAA within neurons and the extracellular space. Excess cerebral NAA induces osmotic imbalance, intramyelinic vacuolation, and impaired myelination [6]. More recent studies suggest a direct neurotoxic effect of NAA through interference with glutamatergic transmission and oxidative stress [7].

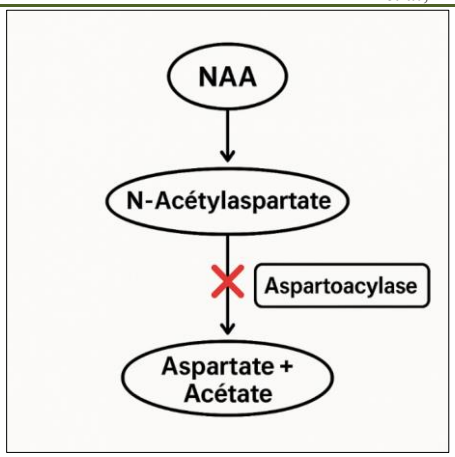


**Figure 3: Blockage of N-acetyl-aspartate (NAA) metabolism in Canavan disease**

This metabolic blockade causes accumulation of NAA in the brain and a deficit in acetate, essential for myelin synthesis, leading to diffuse demyelination.

To date, over 70 different ASPA gene mutations have been reported in the literature [8]. Certain mutations are population-specific, particularly among Ashkenazi Jews, where two founder mutations (E285A and Y231X) account for the majority of cases [9]. In our observation, the identified mutation was a c.924del deletion, causing a frameshift and complete loss of enzymatic function. This mutation is associated with the severe infantile form of the disease, consistent with our patient's clinical presentation.

Clinically, Canavan disease usually manifests as a severe infantile form. The first symptoms appear between three and six months of life: axial hypotonia, global psychomotor delay, lack of head control, and poor sucking [10]. Progressive macrocephaly, often due to megalencephaly, is a major sign observed in nearly 80% of patients [11]. The disease progresses with secondary spasticity, epileptic seizures, and progressive visual impairment leading to optic atrophy [12]. The prognosis is poor, with most children dying within the first decade, mainly due to respiratory or nutritional complications. However, a few cases of survival into the second or even third decade have been reported [13].

Our patient exhibited all of these characteristic features: early axial hypotonia, absence of head control, global motor delay, generalized seizures, and rapidly progressive macrocephaly. Neurological examination showed brisk deep tendon reflexes and emerging peripheral hypertonia, indicating transformation from a hypotonic to a pyramidal syndrome—typical of the disease's progression [14]. The suspected optic atrophy observed during ophthalmological evaluation is also frequently reported [15].

Magnetic resonance imaging is a key diagnostic tool. The abnormalities are typical: diffuse, symmetrical T2-weighted hyperintensities of the white matter, predominantly in subcortical regions, with relative preservation of the basal ganglia, brainstem, and cerebellum [16]. The MRI of our patient was entirely consistent, strongly suggesting a spongiform-type leukodystrophy. Magnetic resonance spectroscopy (MRS) is a noninvasive complementary technique that detects the elevated NAA peak considered pathognomonic of Canavan disease [17]. In our case, MRS could not be performed, but the massive urinary NAA elevation confirmed the diagnosis. Several studies have shown that spectroscopy can reveal metabolic abnormalities even before urinary NAA accumulation, making it a valuable tool for early diagnosis [18].

The biochemical metabolic assessment plays a central role in confirming the diagnosis of Canavan disease. In any suspected leukodystrophy presenting with macrocephaly, axial hypotonia, and developmental delay, urinary organic acid analysis must be performed. In our patient, chromatographic analysis showed a major elevation of N-acetyl-aspartic acid (NAA) reaching 1045 mmol/mol creatinine—more than fifty times the normal value (<20 mmol/mol). This result is highly specific and indicates profound aspartoacylase deficiency. Massive accumulation of NAA in the brain and its increased urinary excretion are pathognomonic of the severe infantile form of Canavan disease [7,10,12].

Literature data confirm a correlation between NAA levels and clinical severity: juvenile forms show moderate increases, whereas infantile forms exhibit much higher values, as in our patient. This observation aligns with biochemical profiles described by Sistermans *et al.,* [10] and Hoshino & Kubota [12].

ASPA enzyme activity measurement in fibroblast cultures or fetal samples (amniocytes, chorionic villi) serves as a complementary reference test. In affected patients, enzymatic activity is nearly absent, whereas heterozygous carriers retain about 50% of normal activity [7,9]. This test confirms the enzymatic nature of the defect and allows prenatal diagnosis [9].

Similarly, urinary aspartic acid—derived from NAA hydrolysis—may be evaluated to estimate disease severity, being markedly higher in infantile forms than in juvenile forms [17,19]. Overall, urinary NAA measurement remains the most rapid, sensitive, and specific diagnostic method, while ASPA activity assays provide biochemical and genetic confirmation. The combination of biochemical and genetic data constitutes the gold standard for diagnosing Canavan disease as well as the search for genetic mutations.

Genetic analysis is now the reference examination, enabling both diagnostic confirmation and family genetic counseling. In our patient, homozygosity for the c.924del mutation of the ASPA gene confirmed the diagnosis. Parental consanguinity and a history of sibling death perfectly illustrate the autosomal recessive inheritance pattern.

Canavan disease must be differentiated from other leukodystrophies associated with macrocephaly and psychomotor delay. Alexander disease is characterized by Rosenthal fiber deposits and predominant frontal involvement on imaging [20]. Glutaric aciduria type I also associates macrocephaly and delay, but imaging shows pericerebral space dilatation and putaminal involvement [21]. Krabbe disease and Pelizaeus-Merzbacher disease also enter the differential diagnosis, but the detection of massive urinary NAA excretion remains specific to Canavan disease [22].

Management remains essentially symptomatic and multidisciplinary. It includes motor and respiratory physiotherapy, nutritional follow-up, antiepileptic treatment, and prevention of infectious complications [23]. In our patient, early functional rehabilitation was implemented, and enteral feeding via nasogastric tube was established due to dysphagia. The unfavorable outcome observed mirrors that commonly reported in the literature, where most children develop severe respiratory or nutritional complications leading to early death.

The absence of curative treatment has prompted exploration of several innovative therapeutic strategies. Among them, gene therapy appears the most promising. Trials using adeno-associated viral vectors to deliver a functional copy of the ASPA gene have shown reduced cerebral NAA and partial remyelination improvement in animal models [24]. Clinical trials in humans have demonstrated feasibility and safety, though clinical benefits remain modest [25]. Other potential approaches include acetate supplementation or acetate precursors to compensate for substrate deficiency in myelin synthesis [26], and oligodendroglial stem cell transplantation to restore myelination [27]. These remain experimental but offer hope for the future.

Our observation highlights the importance of rapidly considering Canavan disease when confronted with axial hypotonia, macrocephaly, and developmental delay. Early diagnosis allows not only improved symptomatic management but also targeted genetic counseling and family screening, particularly crucial in regions with frequent consanguinity such as Morocco.

## CONCLUSION

Canavan disease is a rare and severe hereditary leukodystrophy characterized by diffuse spongiform degeneration of white matter, resulting from aspartoacylase deficiency and pathological accumulation of N-acetyl-aspartic acid. It typically manifests during infancy with axial hypotonia, global psychomotor delay, progressive macrocephaly, and later spasticity, seizures, and visual impairment. Diagnosis is based on clinical, radiological, and biochemical data and must be confirmed by ASPA gene analysis.

The reported case illustrates the classical infantile presentation with an unfavorable course despite multidisciplinary symptomatic care. It underscores the importance of early diagnosis, especially in consanguineous populations where recurrence risk is high. Genetic counseling and family screening are therefore essential.

Although no curative treatment currently exists, advances in gene therapy and regenerative medicine offer promising perspectives, making Canavan disease a model of research for leukodystrophies.

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