# The Diagnostic Process of an Ultra-rare Disease: Free Sialic Acid Storage Disorder (Salla Disease) in a 11-Month-old Infant, a Case Report

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## Keywords

Neurodevelopmental impairment ; lysosomal storage disease ; neurometabolic disorder ; free sialic acid storage disease ; Salla disease ; pediatric global developmental delay.

## Introduction

Imagine the challenge: recognizing deviation from the norm. In pediatric medicine, we often encounter impaired cognitive and motor development. Although rare, metabolic disorders remain an important cause, accounting for 1-5% of patients with neurodevelopmental disorders (1). Successful diagnosis of developmental delay acknowledges the balance of allowing for borderline natural cognitive and motor progression while simultaneously identifying a potential aberrant course of pediatric development (2). The entire process of neurodevelopmental evaluation, aside from diagnostic testing, is time consuming. This case report illustrates the diagnostic process, the importance of considering metabolic disorders in the differential diagnosis, and the contributory potential of comprehensive genetic investigation in a patient with neurodevelopmental disorder caused by Salla disease, a rare free sialic acid storage disorder (FSASD).

## Case description

An 11-month-old male infant presented to a secondary care center with severe cognitive and motor developmental delay. Concerns had been reported by the mother since 6 months of age, as he remained unable to sit unsupported. Despite the initiation of physiotherapy, there was no developmental progress. At the age of 11 months, the neuropsychological assessment corresponded to a 4-month-old infant in cognitive and motor development. In the absence of paternal information, the family history was negative. The mother reported substance abuse (tobacco, cannabis, amphetamine) during pregnancy. Fetal growth assessments were performed only in the third trimester and showed no abnormalities. He was born at a gestational age of 39 weeks and 2 days, APGAR was 9 and 9, with a birth weight of 3295 grams. Newborn screening showed no abnormalities. On examination, the blond-haired, blue-eyed boy smiled interactively and produced high-pitched sounds. Clinical examination revealed only mild facial dysmorphism, including bilaterally protruding ears with low insertion and a high palatal arch without evidence of organomegaly. Biometric data of weight, height, and head circumference were within the normal standard deviation. He preferred the supine position and was able to lift his head from his chest in the prone position. Although he could track objects within his field of vision, he was unable to reach purposefully, sit unsupported, or roll over. Neurologic examination, including ophthalmologic examination, revealed horizontal nystagmus, truncal hypotonia, clenched fists, hyperkinetic movements of the arms, increased muscle tone in the legs, and ataxia of the upper and lower limbs. Audiologic evaluations were normal.

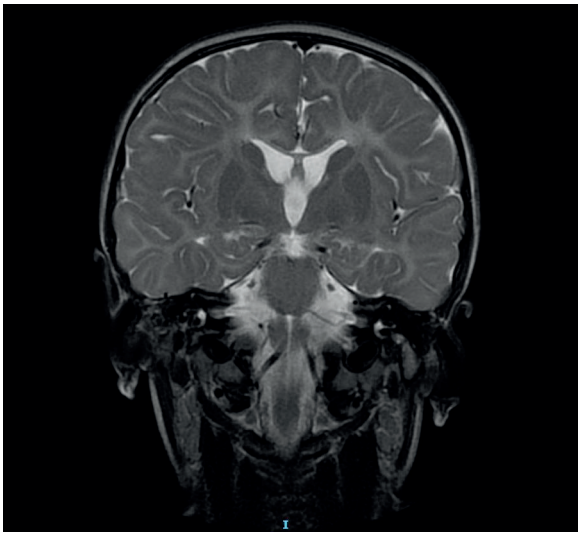
### *Biochemical analysis*

Blood tests were negative for congenital infections, endocrine, renal, hepatic and metabolic disorders including amino acids, acylcarnitines, ceruloplasmin, copper, glycosylation defects, homocysteine. Urine toxicology was negative, but metabolic analysis including organic acids, purines, pyramidines, creatines, oligosaccharides, mucopolysaccharides, $\alpha$-amino-adipic semialdehyde, and sialic acid was abnormal. Since the detection of elevated free sialic acid and markers of (galacto-)sialidosis were not in the range of (galacto-)sialidosis patients, it was initially considered abnormal due to young age and nutrition. However, repeated urine analysis, in addition to the genetics, showed a threefold increase in sialic acid levels.

### *Radiological imaging*

Skeletal radiography was not performed. Cerebral MRI revealed hypomyelination of the basal ganglia and hypoplasia of the corpus callosum (Figure 1).

**Figure 1**: Cerebral MRI showing hypomyelination of the cortex and basal ganglia as well as a thin or hypoplastic corpus callosum



### *Genetic analysis*

Following the recommendations of the Dutch guideline on diagnostic investigation in pediatric neurodevelopmental disorders, we performed a SNP array and a Fragile X panel, which showed no abnormalities. The patient was referred to a clinical geneticist at Erasmus University Medical Center. Considering the clinical presentation, the lack of paternal information and the uncertainty regarding the interpretation of the initial metabolic urine analysis, a comprehensive genetic evaluation for genetic and metabolic disorders by whole exome sequencing (WES) of the index patient and the mother was recommended. In January 2022, a homozygous mutation of the *SLC17A5* gene responsible for FSASD was identified, confirming the diagnosis of Salla disease.

### *Patient follow up*

In parallel with the diagnostic process, rehabilitation efforts, including physical therapy, were initiated to stimulate motor development and to assess the need for specific outpatient developmental support. The patient was referred to a pediatric neurologist and metabolic pediatrician at the Center for Lysosomal and Metabolic Diseases, along with a pediatric gastroenterologist, pediatric cardiologist, and orthopedic surgeon. Cardiac ultrasound showed no cardiomegaly and electroencephalogram showed no evidence of epilepsy. In addition, multidisciplinary care included regular follow-up with a general pediatrician, ophthalmologist, rehabilitation physician, dietitian, speech therapist and social worker. Therapeutic options within the spectrum of FSASD include primarily supportive care, as curative treatments are not available. Prognosis includes regression of cognitive and motor skills after puberty, with severity related to genotype, and reduced life expectancy.

## Discussion

In general, the identification of neuropsychological abnormalities in children begins primarily with parental and/or primary care concerns about cognitive and motor development. Although less common, we emphasize the need to consider metabolic disorders as a potential diagnosis in the group of neurodevelopmental disorders (2). Investigation of all medical etiologies (Table 1) could prolong the duration of the diagnostic phase. Thus, the question arises as to how ONE systematically aproaches the diagnostic process of a child with a neurodevelopmental disorder in order to minimize diagnostic delay. While there are national guidelines for the diagnostic approach to pediatric neurodevelopmental disorders (e.g., the Netherlands), there is still a need for an international guideline with widely accepted recommendations (2).

We strongly recommend the early involvement of pediatric experts in metabolic disease, neurology, and genetics to assist in the selection and sequencing of complementary investigations, in addition to history, physical examination, and neuropsychological assessment. In addition, evaluation for possible multi-organ involvement (e.g., visual, auditory, cardiac, hepatic, orthopedic) is necessary and should be systematically repeated to monitor progression over time (2, 3). Salla disease is an autosomal recessive neurodegenerative lysosomal storage disorder. Mutations of the *SLC17A* gene on chromosome 6q13 account for the spectrum of FSASD (3, 4). The global prevalence of Salla disease is less than 1 in 1,000,000. However, in Finland it is estimated to be 0.1%, with an incidence of 1 in 42,000 (5, 6). The *SLC17A5* gene encodes for sialin, which facilitates the transfer of intra- and intercellular metabolites, including free sialic acid. Dysfunctional sialin contributes to the accumulation of free sialic acid and N-acetyl-neuraminic acid (NANA), which is predominantly localized in the lysosome (4, 5).

The pathogenic mutation correlates with the severity of the FSADS phenotype (Table 2) (3, 7, 8). Clinical features of FSADS include dysmorphism (e.g., blue eyes, hypertelorism), growth retardation, recurrent respiratory infections, cardiomegaly, renal disease, inguinal hernia, skeletal dysostosis, ophthalmopathy (e.g., optic atrophy, strabismus, corneal clouding), intellectual disability, and neurological symptoms such as nystagmus, muscular hyper- and hypotonia, athetosis, and ataxia. Forty percent of individuals with infantile sialic acid storage disease develop epilepsy (3, 8, 9).

**Table 1:** List of potential etiologic medical conditions in neurodevelopmental disorder.

| |
|---|
| Renal disease |
| Liver disease |
| Neurological disease |
| Endocrine disorders |
| Metabolic disease (including mitochondrial disorders) |
| Genetic disorders |
| Teratogenic factors (e.g. maternal medication/intoxication) |
| Congenital factors (e.g. perinatal infection, neonatal complications) |

**Table 2:** Genotype-Phenotype correlation.

| **Genetic mutation** | | |
|---|---|---|
| Phenotype | Mild (Salla) | Homozygote missense p.Arg39Cys |
| | Intermediate | Heterozygote p.Arg39Cys and *SLC17A5* variant |
| | | Heterozygote p.Arfg39Cys and homozygote p.Lys136Glu |
| | Severe (ISSD)* | Heterozygote non-p.Arg39Cys *SLC175A5* |

*ISSD: infantile sialic acid storage disease

Cerebral MRI often shows cortical atrophy, hypomyelination, and hypoplasia of the corpus callosum, resulting in motor and cognitive disability. One third of patients will be unable to walk. Although the mean IQ of 40 severely limits the ability to learn, receptive comprehension exceeds speech production ($p = 0.003$), facilitating the ability to communicate (8). Impaired language production was significantly associated with phenotype ($p = 0.003$) (8). Overall, the prospects for independent living without assistance are negligible (8, 9).

Although the gold standard for FSASD remains unknown, the urinary or cellular detection of lysosomal free sialic acid is considered pathognomonic for FSASD (3). Prior to the introduction of WES, a cohort study of 116 patients showed that 70% were diagnosed by urine biochemical analysis alone (10). However, the absence of biochemical detection of free sialic acid does not exclude the diagnosis of FSASD, as interfering urinary substances could potentially lead to false negatives (3, 10, 11).

In accordance with current recommendations, we advocate the use of genetic diagnostics as clinical presentation and biochemical results may be inconclusive (3). To determine whether to pursue targeted gene panel testing when a specific disorder is suspected or broad WES, we recommend a multidisciplinary review of individual features by experts in pediatric neurology, metabolic disease, and clinical genetics.

All FSASD cases report a delay in diagnosis, estimated at 2.5 years and a median age at diagnosis of 3 years (10) . However, in our case, the diagnosis was made in 13 months and the patient was 25 months old. Collaborative efforts among medical professionals from multiple centers to centralize patient care and diagnosis in a single institution may have reduced the diagnostic delay.

There are no curative or preventive treatments for FSASD. Supportive care with appropriate diagnostic testing focuses on neurologic, ophthalmologic, and cardiac morbidity, nutritional support, family support, and prenatal counseling of parents (3, 8, 9). Despite the degenerative nature of the disease, motor development continues into the twenties and cognitive development into the thirties (8, 9). Neurocognitive impairment at the time of diagnosis significantly affects future developmental potential. Life expectancy at birth is significantly reduced in all phenotypes of FSASD, with a average survival of 57 years for female patients and 59 years for male patients (9). Survival may be correlated with the level of urinary sialic acid excretion at diagnosis, with significantly improved survival when the level is <6 times elevated (10).

## Conclusion

The consideration of metabolic disorders remains essential in the differential diagnosis of children with neurodevelopmental disorders. This case contributed to the understanding of the diagnosis of the ultra-rare spectrum of FSASD. We anticipate the development of an international guideline for the diagnosis of pediatric neurodevelopmental disorders in the near future.

## Competing interests

The authors state no conflict of interest.

## Informed consent

Informed consent was obtained from the patient.

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