Case Report

An Unusual Developmental Profile of Salla Disease in a Patient with the SallaFIN Mutation

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Received 6 October 2012; Accepted 30 October 2012

Academic Editors: J. Lazareff and I. L. Simone

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Salla disease (SD) is a disorder caused by defective storage of free sialic acid and results from mutations in the \( SLC17A5 \) gene. Early developmental delay of motor functions, and later cognitive skills, is typical. We describe a developmental profile of an unusual homozygous patient, who harboured the SallaFIN (p.R39C) mutation gene. The study involved neurological examination, neuropsychological investigation, and brain imaging. The neurocognitive findings were atypical in comparison with other patients with the SallaFIN mutation. Interestingly, there was no deterioration in the patient's neurological condition during adulthood. Her neurocognitive skills were remarkably higher than those of other patients with a conventional phenotype of SD. Our results suggest that the phenotype of SD is broad. Unidentified genetic or environmental variation might explain the unique SD type of this case.

1. Introduction

Salla disease (SD; OMIM 604369) is a disorder characterised by defective storage of free sialic acid and belongs to the Finnish disease heritage [1]. However, sporadic cases of SD have been reported in many countries. The disease is caused by mutation of the \( SLC17A5 \) gene, which encodes a protein that transports sialic acid across the lysosomal membrane [2].

Salla disease affects the white matter by causing dysmyelination of the central nervous system and the peripheral nervous system. Magnetic resonance imaging studies have shown dysmyelination of the entire white matter of the cerebrum [3]. Cerebellar involvement has also been reported [4]. Hypoplasia of the corpus callosum is a typical finding in patients with SD. A conventional subtype and a severe subtype of the disease have been identified [5].

In neurocognitive terms, SD impacts nonverbal performance more than linguistic ability [6]. The common features related to nonverbal learning disabilities are associated with dysmyelination of the white matter. Another typical pattern seen in patients with SD is severe motor disability. After the second decade of life, the decline in motor skills is usually more pronounced than that in cognitive function. All affected individuals are intellectually disabled, but the level of cognitive and motor disabilities varies notably among patients with SD.

It is estimated that 95% of Finnish patients with SD are homozygous for the SallaFIN mutation: the p.R39C allele of the \( SLC17A5 \) gene [7]. Only a few patients are compound heterozygotes. These patients harbour the SallaFIN mutation in one allele of \( SLC17A5 \) and a different mutation in the other. Compound heterozygotes have a more severe phenotype than homozygotes [5]. Here we describe a patient with
the homozygous SallaFIN mutation. Her neurocognitive
development is unusual when compared with that of other
patients with the same phenotype.

2. Case Presentation

The proband is a 30-year-old woman. She was born after
an uneventful pregnancy at full term. Her parents were
nonconsanguineous. SD was diagnosed at 3 years of age on
the basis of clinical symptoms and increased level of free sialic
acid in the urine.

The patient’s development during the first year of life was
relatively normal, but crawling was unstable and muscular
hypotonia and nystagmus were noticed. The patient spoke
her first words at 1 year of age and her first sentences at 2
years of age. She learned to walk by 1.5 years of age, but
her gait and balance were abnormal. At 3 years of age, her
cognitive development was assessed as normal, except for
mild slowness and clumsiness when performing fine motor
skills. The followup evaluations showed mild delays in motor
tasks, eye-hand coordination, and concentration. Her verbal
development was slightly delayed, and verbal dyspraxia was
reported. At 6 years of age, the developmental delay was
approximately 2 years.

Inattentiveness, hyperactivity, and problems with sleep
were reported during childhood. The patient also had prob-
lems with balance and body awareness. Ataxic symptoms
were prominent in childhood, but improved during the
teenage years.

During her school years, the neurocognitive development
fluctuated notably. Verbal performance was consistently bet-
ter than visual performance or fine motor skills. Intellectual
disability was considered to be mild.

At the age of 12 years, the patient’s verbal skills, as
assessed using the Wechsler Intelligence Scale for Children-R
test [8], were at the level of a 7 year old, and her performance
skills varied between those typical of a child of 5 years 6
months and 6 years 6 months of age. Two years later, her
verbal skills had improved. At 14 years of age, no progression
was noted in the neurocognitive deficits. The developmental
age of the patient varied between 4 and 8 years, and her verbal
skills were notably better than her motor and visual abilities.

2.1. Neurological Examination. At the age of 30 years, the
proband was living alone with support. She was a social
person, keen on the arts and team sports. She was 157 cm
in height and weighed 56 kg. She was taking no medications.
On examination, auscultation of the heart and lungs was
unremarkable, her blood pressure was 114/74 mmHg, and
the electrocardiogram was normal. Her facial features were
slightly coarse. The proband could walk without aid, but
both legs were in a pes planus position. When walking, she
had some athetotic movements in her upper extremities.
Muscle strength and skin sensation were normal, tendon
reflexes were symmetrical and normal, and the plantar
responses were in flexion. Both Achilles tendons were
slightly shortened and there was mild spasticity in both
legs. Neurological examination revealed only mild ataxia.

There was mild instability in the Romberg test and the
patient was unable to stand with her eyes closed. There
was no ataxia or dysmetria shown by coordination tests,
but her hand movements were clumsy. She suffered from
marked myopia and used six dioptre corrective lenses. Clear
outward strabismus was seen in her right eye. However,
the eye movements were normal and nystagmus was not
detected. The neurological condition of the patient had not
deteriorated during the previous 10 years.

There had been no deterioration of the patient’s motor
skills in adulthood. Her skills had improved with respect to
balance, coordination of body movements, and reciprocal
motor actions, as well as processing the sequences of
movements. The speed of motor actions had become slightly
slower during the last few years.

The electroencephalogram (EEG) was normal at 3 years
of age, but showed mild generalized background abnormality
with occasional spikes and sharp waves at the left temporo-
parieto-central region at 5 years of age. Quantitative EEG was
normal at 15 years of age. There was no history of epileptic
seizures, but symptoms that resembled the startle reflex were
noticed in response to sudden noises.

2.2. Neurocognitive and Motor Development. The methods
that were used for neuropsychological evaluation of the
patient are presented in Table 1. Her developmental age,
as assessed by Wechsler Intelligence Scale for Children-III
[9] at the age of 30 years, was 7 years 9 months for the
verbal scale and 5 years 4 months for the perceptual scale.
Her neurocognitive performance was remarkably better than
those of other patients with the conventional type of SD and
the SallaFIN mutation [6]. Other patients with SD (n = 37)
have been evaluated using the Bayley Scales of Infant
Development-II [14], because the tasks that are used in the
Wechsler children’s tests were too demanding.

There was a slowing in visuomotor speed as well as eye-
hand coordination during the followup of our patient after
her teenage years. Visual reasoning and spatial orientation
were mildly delayed, and the visuoconstructive skills were
diminished. However, verbal skills had improved. Repetition
of nonsense words and otor motor sequences were difficult for
the proband because of verbal and oral dyspraxia, but the
proband was able to learn and repeat long, logical stories. She
had difficulties with time orientation.

Motor problems were evident but the symptoms had
not progressed during the followup. The proband was
able to walk on the toes and sides of the feet, but the
forward tandem walk was insecure, and motor persistence
and motor coordination were clumsy. Static cerebellar tests
were performed quite well, with only slight problems with
balance. Two of the dynamic cerebellar tests—finger-to-
thumb tapping and toe tapping—were performed slowly but
correctly. Visuomotor deficits were evident, but the proband
managed the test of basic functional mobility quite well.

2.3. Brain Imaging. Brain imaging performed at 15 years
of age showed dysmyelination. The corpus callosum was
hypoplastic, but the cerebellum, pons, and the proximal part
Table 1: Neuropsychological evaluation of the proband at 30 years of age.

<table>
<thead>
<tr>
<th>Full name of the test</th>
<th>Abbreviation</th>
<th>Reference</th>
<th>The domain of the test/chosen parts</th>
<th>Resultsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children's Neuropsychological Test Battery</td>
<td>NEPSY</td>
<td>Korkman et al. (1997) [10]</td>
<td>*Perceptual skills</td>
<td>1</td>
</tr>
<tr>
<td>Physical and Neurological Examination of Soft Signs</td>
<td>PANESS</td>
<td>Denckla (1985) [11]</td>
<td>*Comprehension of instructions</td>
<td>0</td>
</tr>
<tr>
<td>Static and Dynamic Cerebellar Tests</td>
<td>Cerebellar tests</td>
<td>Fawcett et al. (2001) [12]</td>
<td>*Oromotor sequences</td>
<td>2</td>
</tr>
</tbody>
</table>

a = among average, 1 = mild deficits, 2 = severe deficits.

3. Discussion

The typical neurocognitive profile of SD consists of a lower level of nonverbal performance as compared with linguistic skills. Findings related to nonverbal learning disabilities have been outlined [6]. Herein, we have described an unusual developmental profile of SD in a patient with the SallaFIN mutation. Her neurocognitive development differs from that of other patients with SD of the conventional subtype who carry the SallaFIN mutation. Her neurological condition has remained fairly constant during adulthood. Only mild progression of the symptoms related to her neurocognitive skills has been seen. The MRI findings showed that the ventricles were of normal size; the corpus callosum was thin, but there was no cortical atrophy.

The patient has received regular physiotherapy and has participated actively in sports since childhood. The benefits to the brain of physical activity, which include anatomical, functional, and molecular changes, have been documented [15]. Physical activity also affects the health of the neural network and on the capacity to process information.

Unknown genetic and environmental variation might explain the unique SD type of the proband. The heterogeneity of the severity and progression of SD is a challenge for diagnostic work and rehabilitation with both children and adult patients.

Acknowledgments

The study was supported by Finnish Brain Foundation, Finnish Cultural Foundation, and Maire Taponen Foundation.

References


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