Salla disease in Turkish children: severe and conventional type

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Sialic acid storage disorder, known as Salla disease, is a rare autosomal recessive lysosomal disorder produced by a defect of a proton-driven carrier that is responsible for the efflux of sialic acid from the lysosomal compartment. We report two patients with Salla disease: a two-year-old girl, presented with hypotonia, inability to speak and walk, bilateral optic atrophies, defective myelination, cerebellar atrophy, and thinning of the corpus callosum on magnetic resonance imaging (MRI), who was classified as intermediate severe Salla disease; and a four-year-old girl, presented with relatively late-onset, slight hypotonia, and delayed language and mobility development, and supported by relatively protected MRI findings, who was classified as conventional Salla disease. Diagnosis of Salla disease was confirmed by accumulation of sialic acid in fibroblast culture: 15.1 and 13.2 nmol/mg protein in the first and second patient, respectively. Optic atrophy observed in the first case may be an additional feature besides the characteristic manifestations of Salla disease.

Key words: Salla disease, severe type, conventional type, optic atrophy.

The lysosomal free sialic acid storage diseases include the recessively inherited allelic neurodegenerative disorders Salla disease (SD) and infantile sialic acid storage disease (ISSD), in which the free sialic acid transport from lysosomes is defective. The conventional form of SD, which is established in the Finnish population, represents the mildest end of the clinical spectrum. The phenotype is characterized by a slowly progressive course with hypotonia, ataxia, developmental delay, and slightly decreased life expectancy[1]. An intermediate severe form of SD, reported in some cases with a variety of ethnic backgrounds, is characterized by an earlier onset of symptoms, seizures, inability to walk, and shortened life span[2]. In spite of the fact that ISSD shares the same biochemical abnormality and allelic mutation with SD, it is clinically distinct and very serious. Visceromegaly, coarse facial features, failure to thrive, and early death are its main features[3]. Unlike SD, ISSD has been reported throughout the world[4].

Here, we report the first Turkish SD patients: the first evaluated as "intermediate severe SD" with a unique optic atrophy and the second as "conventional" type SD.

Case Reports

Case 1

A two-year-old girl was born at term with birth weight of 3,600 g. There was consanguinity between parents. On her physical examination, her weight was 10,500 g (3-10 percentile), height 85.5 cm (25-50 percentile) and head circumference 45.5 cm (25-50 percentile). Neurological assessment revealed muscular hypotonia, brisk tendon reflexes, truncal ataxia, and bilateral optic atrophy. No coarse appearance or visceromegaly was found. Magnetic resonance imaging (MRI) demonstrated abnormally high signal intensity of both cerebral and cerebellar white matter on T2-weighted images. The corpus callosum was thin particularly on the anterior area. There was a cerebellar atrophy (Fig. 1).

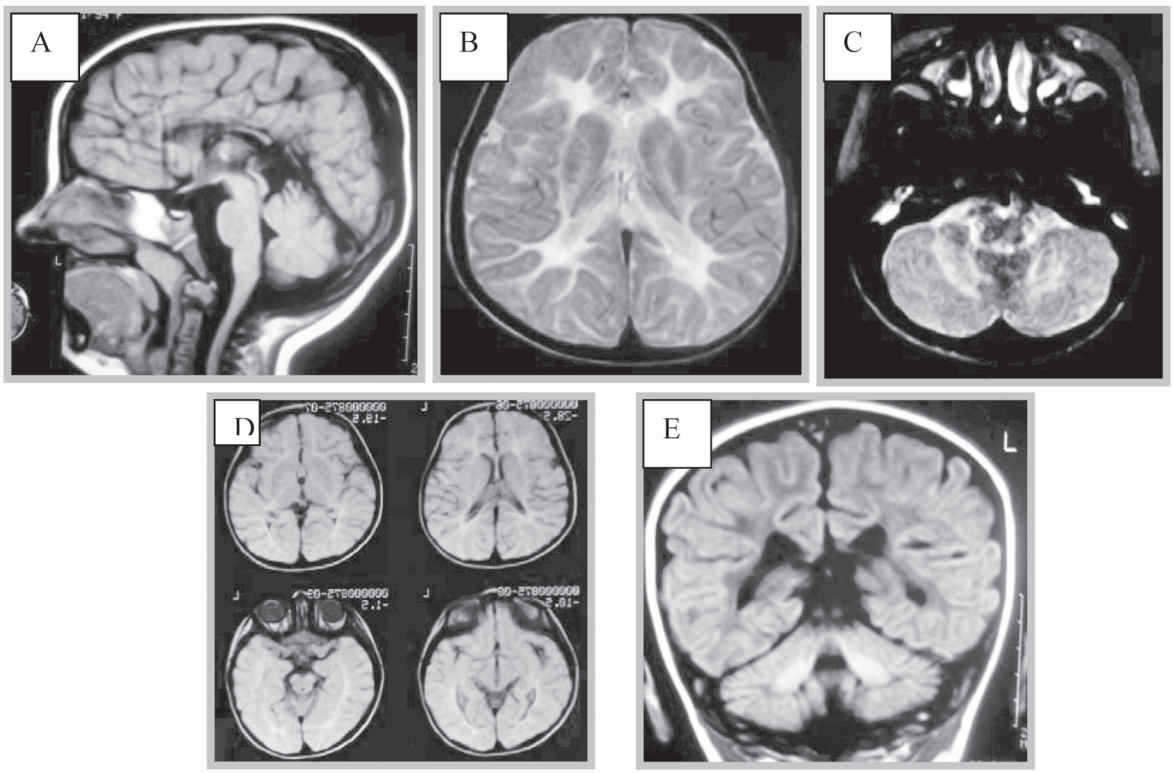

Fig. 1. Case 1: A two-year-old girl with clinically severe Salla disease.
A- T1–weighted MR images: at the age of two years, the corpus callosum was extremely thin in the anterior area;
B- T2-weighted MR images: homogeneous high signal intensity in the central cerebral white matter including the internal capsules as a sign of hypomyelination;
C- T2-weighted MR images: high signal intensity in the cerebellar white matter;
D- and E- Flair image sequences demonstrated involved u-fibers and homogeneous high signal in cerebral and cerebellar white matter.

Visual evoked potentials demonstrated a partial conduction defect; electroencephalography (EEG) and electromyelography (EMG) were normal. During the next 10 years of follow-up, the child showed an extremely slow progression of psychomotor development, achieving an ability to sit with support at the age of three years and without support at the age of four years. At the age of six years, she achieved a standing with support. She had never walked and never suffered from seizures. At the age of 12, she was wheel-chair dependent. Verbal function was limited to understanding without speaking.

Case 2

The second patient was admitted to the metabolic unit at the age of four years because of impaired speech and ataxia. She was the second child of consanguineous parents. Her history revealed a developmental delay with head control at 4.5 months, unsupported sitting at 14 months, and walking at 2.5 years with prominent athetosis. Her weight was 15,000 g (25-50 percentile), height 88.9 cm (<3 percentile) and head circumference 47 cm (50-75 percentile) on physical examination. Slightly coarse appearance with broad face, flat nose bridge and high arc were noted. Her neurological evaluation revealed a mild mental retardation and ataxia. No visceromegaly or ophthalmological pathology was detected. MRI demonstrated normal T1 and T2 signal intensity of cerebral white matter. The corpus callosum was slightly thin with normal cerebellum (Fig. 2). EEG and EMG were normal. During her four years of follow-up, she learned to say a single word at the age of 2.5 years and at the age of 8 years she uttered only three words. Her receptive language development was better than speech production.

A wide panel of metabolic investigations was negative or normal for both patients. The urine scan for glycosaminoglycans revealed no pathology, whereas sialic acid excretion in urine

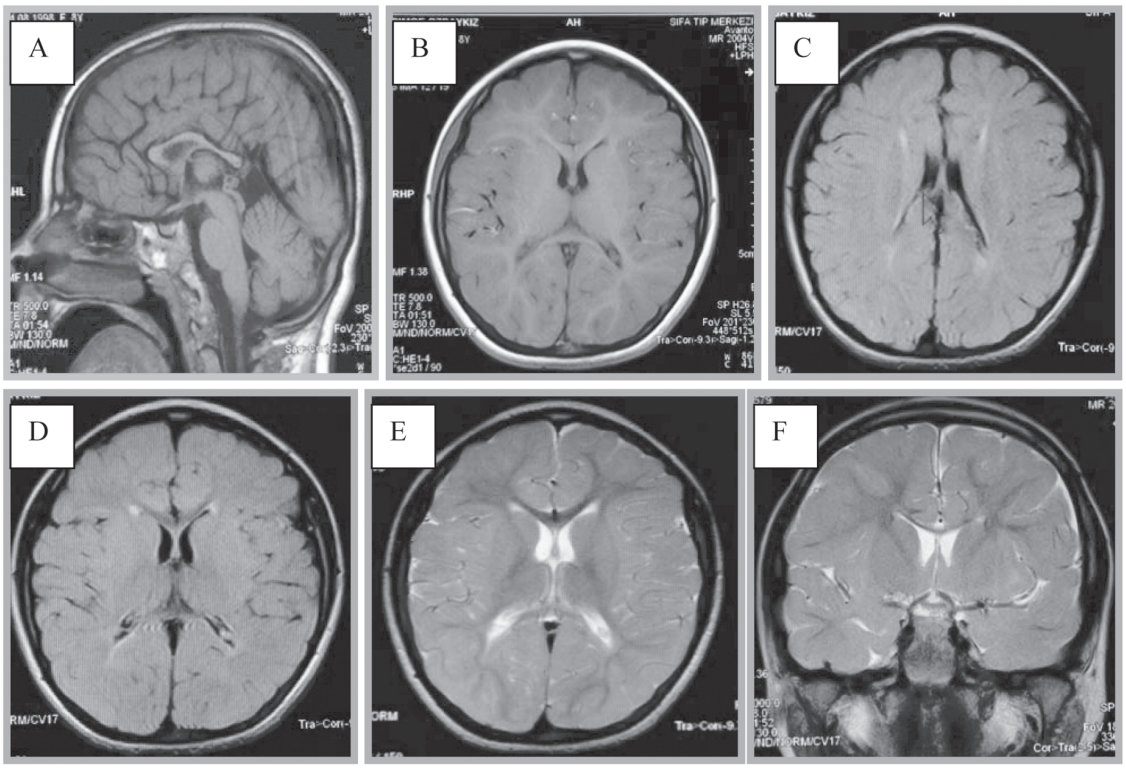

Fig. 2. Case 2: A four-year-old girl with clinically mild Salla disease.
E-T1–weighted MR images: at the age of four years, the corpus callosum was slightly thin;
F-and C- T2-weighted MR images: there was no significant change in the signal intensity as a sign of hypo or dysmyelination;
D-E-F- Flair image sequences demonstrated intact u–fibers and normal cerebral white matter.

was 201 mmol/mol creatinine in the first case and 167.4 mmol/mol creatinine in the second case (controls <55 mmol/mol creatinine). Thereafter, confirmatory fibroblast culture demonstrated accumulation of sialic acid (15.1 and 13.2 nmol/mg protein, respectively; control: 1.2-2.9 nmol/mg protein). Considering the clinical features and developments during the follow-up period, our first reported case was evaluated as intermediate severe, while the second patient was considered conventional type SD.

Discussion

Free sialic storage diseases (SD and ISSD) are rare autosomal recessive disorders resulting from mutations in SLC17A5, a gene that codes sialin, a lysosomal membrane sialic acid- transporting protein. Despite the fact that the first reported patients with SD originated from Finland and Sweden, cases from different European countries (Italy[5], Denmark[6], England[7], and France[8]), Asia (Japan[9]), and America (USA[2]) have been published recently.

Functional studies aimed at elucidating the pathophysiology of sialic acid transport have been reported recently[10]. It has been suggested that the absence of hydrops fetalis, hepatosplenomegaly, dysostosis multiplex, and early lethality, which are peculiar to ISSD, correlates with the presence of a residual transport activity[11]. In agreement with this hypothesis, values of free sialic acid found in our patient's fibroblasts correlated with SD range and were below the ISSD range (10.0±2.9 and 139±92 nmol/mg protein, respectively) (Fig. 3). Highly severe clinical manifestations presented in our first case reflected a phenotype intermediated between that of ISSD and SD[12].

Another disease associated with elevated urinary and fibroblast free sialic acid is sialuria. The differentiation between a cytoplasmic (sialuria) and a lysosomal location (SD, ISSD) of free sialic acid is based on subcellular fractionation of sialin accumulated in fibroblasts[13]. Additionally, patients with sialuria have mild clinical findings such as coarse features, hepatomegaly, and relatively normal growth and development

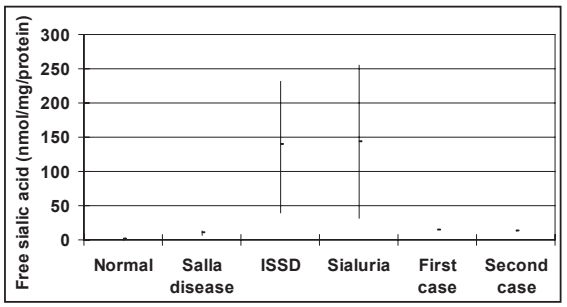

Fig. 3. Free sialic acid levels in fibroblasts. The reference values were taken from published data by Seppala et al. (Seppala R, Tietze F, Krasnewich D, et al. Sialic acid metabolism in sialuria fibroblasts. J Biol Chem 1991; 266: 7456-7461).

without neurological involvement. The prominent neurological findings in the presented cases excluded the possibility of sialuria.

All reported SD cases are intellectually disabled, ranging from moderate to severe mental retardation[14]. The typical cognitive profile of SD patients is characterized by better verbal ability compared with nonverbal functioning, with a peculiar disability of spatial and visuoconstructive functions[3,12]. Difficulties in speech production were strongly associated with phenotypic severity. The majority of the patients (76%) learned to say single words, whereas only 27% of the patients learned to utter sentences[15]. As it was reported, speech comprehension was clearly better than expressive speech ability in our second patient, so it was taken into account in the selection of the rehabilitation program. However, our first patient had never achieved an ability to speak.

Muscular hypotonia, the first symptom observed in the majority of reported patients, was the presenting symptom of our first patient. According to the results found by Varho et al.[15], hypotonia was associated, although not strongly, with a phenotypic severity. Moreover, retarded motor development presented in all of the reported patients existed in our two patients as well.

To our knowledge, optic atrophy detected in SD has not been reported previously. Optic atrophy was reported in patients with ISSD[16], and transient nystagmus was present in 11 of 39 patients (2 of 4 of the severe phenotype) reported by Verho et al.[15]. Pale optic disks were noticed in a case description by Biancheri et al.[5]. Principally, optic atrophy can occur at presentation or during the course of the neurodegenerative disease. Demonstration of optic atrophy may be a clue for diagnosis. However, since peripheral neuropathy has been observed only in this peculiar patient with SD, there is a possibility that this association may be coincidental. We suggest that careful study in this area should be considered in the clinical evaluation of patients with SD.

Brain involvement in SD was described by Haataja et al.[17] and then reviewed in 15 cases by Sonninen et al.[18]. They recognized three different radiologic patterns for cerebral changes: the first, slowly progressive periventricular myelination; the second, homogeneous white matter and myelin in the internal capsules only; and the third: an extremely high periventricular signal intensity on T2-weighted images and the most obvious atrophic changes. Later, studies reported by Biancheri et al.[11] and Linnankivi T et al.[19] revealed the presence of abnormal signal intensity in the cerebellar white matter. Our first case had quite typical MRI findings: homogeneous high signal intensity in the central cerebral and white matter including the internal capsules associated with cerebellar involvement. The second case had no white matter involvement. This correlation between clinical and MRI findings may support the suggestion of Sonninen et al.[18] about the association between the severity of brain involvement demonstrated by MRI and phenotypic severity.

The main limitation of the presented study is the fact that DNA mutation analysis was not available for either patient.

Our reported clinical data may basically be explained by those of recently published experiments investigating the hypothesis about the association between clinical phenotype of sialic acid storage disorders and residual transport activity of sialin, based on accumulated sialin levels in fibroblasts. It was determined that phenotype severity increased in conjunction with increased accumulation of sialin.

In conclusion, SD needs to be considered in the diagnosis of patients with developmental delays, growth retardation, and coarse facies. Lack of Finnish ethnicity should not preclude investigation of free sialic acid storage, which can be pursued by quantitative determination

of urinary free sialic acid and confirmed by sialic acid measurements in cultured fibroblasts and molecular studies. Optic atrophy observed in our first case may be an additional clinical feature in patients with intermediate severe SD. Further collection of data in this specific metabolic disease may clarify our understanding of additional features.

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