Type I Sialidosis: A Clinical, Biochemical and Neuroradiological Study

Silvia Palmeri a Marcello Villanova a Alessandro Malandrini a
Otto P. van Diggelen d Jean G.M. Huijmans d Chantal Ceuterick e
Alessandra Rufa b Danilo DeFalco c Giuseppe Ciacci a Jean J. Martin e
Giancarlo Guazzi a

aInstitute of Neurological Sciences and bDepartment of Ophthalmologic and Neurosurgical Sciences,
University of Siena, and cUnit of Neuroradiology, Regional Hospital, Grosseto, Italy; dDepartment of Clinical Genetics,
Erasmus University, Rotterdam, The Netherlands; eLaboratory of Neuropathology, Born-Bunge Foundation,
University of Antwerp, Belgium

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Abstract
We report biochemical, morphological and neuroradiological findings in a 40-year-old woman affected with type I sialidosis. The clinical symptoms, consisting of a cerebellar syndrome, were first noted at the age of 17 years. The macular cherry-red spot was first observed after 23 years of disease. A CT scan performed at 21 years of age showed enlargement of the fourth ventricle. Nuclear magnetic resonance imaging of the brain performed at the age of 40 showed severe atrophy of the cerebellum and pontine region; atrophy of cerebral hemispheres and of the corpus callosum was also observed. We emphasize the prolonged course of illness in this patient, observed over a long period of time. Of particular interest is the neuroradiological study showing our findings both at the beginning of the disease and after 20 years.

Introduction
Sialidosis is a rare autosomal recessive lysosomal storage disorder due to isolated α-neuraminidase (sialidase) deficiency leading to a defect in the degradation of glycoproteins and accumulation of sialic-acid-containing oligosaccharides and glycopeptides (MIM 256550). Two types can be distinguished: type I sialidosis refers to a slowly progressive syndrome characterized by decreased visual acuity in childhood or juvenile age, macular cherry-red spot, action myoclonus and grand mal seizures; type II sialidosis comprises the severe infantile and congenital phenotypes [1]. Patients with the congenital form show severe non-immune hydrops fetalis and ascites [2], while all patients with the infantile form have a dysmorphic gargoylic aspect, visceromegaly, dysostosis multiplex, macular cherry-red spot and mental retardation. Renal involvement has also been described [3, 4]. Biochemical analysis shows neuraminidase deficiency; however, a residual activity in type I is generally found [1]. The two forms belong to the same complementation group as shown in 1980 [5] and are probably due to different mutations within the same gene.

Dr. Silvia Palmeri
Institute of Neurological Sciences, University of Siena
Viale Bracci 2
I-53100 Siena (Italy)
Tel. +39 0577 585760, Fax +39 0577 40327, E-Mail palmeri@unisi.it
The clinical, biochemical and genetic characterizations of the sialidoses have been complicated by the existence of another disease, galactosialidosis, in which a profound deficiency of neuraminidase is combined with β-galactosidase deficiency. Patients with early infantile, late infantile and juvenile-adult forms of galactosialidosis have been described [6]. Clinically, some forms of this disease overlap with sialidosis.

Type I sialidosis is rare compared to type II sialidosis and galactosialidosis. About 19 confirmed patients, from different ethnic groups, have been described.

Here, we describe an Italian case of type I sialidosis with a long course of illness. Clinical and neuroradiological evaluations at the onset of the disease and 20 years later are described together with the biochemical and morphological data.

Materials and Methods

Case Report

A 40-year-old woman was admitted to our department for stupor accompanied by a long history of blindness, progressive cerebellar ataxia, action myoclonus and generalized convulsive seizures. The family history was unremarkable and the parents were not consanguineous. She was born by normal delivery, and early development was normal. Her progress in school was normal until the last year of high school. Since the age of 17 years, she has suffered from vertigo, unsteadiness with frequent falls, progressive handwriting difficulties and abnormal speech. At 21 years, she experienced two generalized epileptic seizures. Neurological examination at that time revealed normal somatic appearance and normal intelligence. Horizontal nystagmus in the lateral gaze and cerebellar-type dysarthria were observed. Speech was disturbed by facial myoclonus. Hypotonia was also observed, along with action myoclonus in both hands and ataxic gait. Muscle strength was normal and deep tendon reflexes were hyperactive in all four extremities. An ocular examination showed a visual acuity of 15/20 in both eyes. Eye movements were normal. Anterior segments were normal and lenses were clear. The fundus showed a normal aspect. The brain CT scan was normal except for a slight enlargement of the fourth ventricle and cisterna ambiens (fig. 1). An EEG showed the presence of spikes preceding myoclonus in both arms during REM sleep. The patient was placed on a regimen of clonazepam, phenobarbital, carbidopa and L-5-hydroxytryptophan. The generalized seizures remained very rare, but all other symptoms gradually worsened. At the age of 23 years, the patient was severely depressed. From the same age, visual acuity progressively decreased. An ocular examination performed at that time disclosed bilateral punctate lens opacities and fundoscopy demonstrated an irregular foveal reflex, but an electroretinogram and visual-evoked potentials were normal. An assay for neuraminidase performed on leucocytes showed a slight reduction of activity, which was not considered significant at that time. This result was probably due to a technical problem. An EEG showed 9 c/s background activity with rare discharges of sharp waves in anterior regions; frequent diffuse theta waves were also recorded. Audiometric examination gave normal results. At 27 years, the patient was unable to walk without support due to myoclonic jerks and severe ataxia. Visual acuity was 20/200 in both eyes. Fundus examination did not reveal new abnormalities and the peripheral neurophysiological examination was normal. Neuropsychological tests revealed moderate depression and slight mental deterioration, but the co-operation of the patient in the neuropsychological tests was limited by the visual and motor impairment. The symptomatology subsequently progressed very slowly; the patient became wheelchair-bound and was able to walk only briefly with support.

Between the age of 27 and 40 years the patient was not seen. A month before the last admission, at the age of 40, she presented feeding difficulties, became drowsy and confused. Upon examination, she was still drowsy and carried out simple commands if aroused by repeated stimulation. The laboratory tests showed a metabolic condition of hyperosmolarity and dehydration. When her metabolic condition improved, the patient became alert and co-operative, showing moderate mental deterioration. A slow horizontal nystagmus was present, speech was explosive with nasal timbre, lack of co-ordination was observed, and action myoclonus was present in both hands, in facial muscles and the tongue. Muscle strength was decreased in all limbs, and deep tendon reflexes were hyperactive. There was no sensory loss. Routine laboratory tests and ECG were normal, as well as karyotype and plasma amino acids and transferrin. The lysosomal enzymes performed on leucocytes (α-fucosidase, α-galactosidase, β-galactosidase, α-N-acetylgalactosaminidase, β-hexosaminidase A and B, β-glucuronidase, arylsulphatase A and B) were normal as well.

On the EEG, background activity was 6 c/s with frequent theta waves (4–5 c/s) in both parietal-occipital regions. Bone marrow examination did not show histiocytes with storage material. Brain MRI showed severe atrophy of the cerebellar vermis, cerebellar hemispheres and the pontine region. Cortical atrophy of cerebral hemispheres and of the corpus callosum together with enlargement of...
**Fig. 2.** Brain MRI of the patient at the age of 40. 

- **a** Sagittal T$_1$-weighted MR image showing cortical atrophy, atrophy of the cerebellum and of the corpus callosum.
- **b** Axial T$_2$-weighted MR image showing severe cortical atrophy with enlargement of Silvio’s scissure and lateral ventricles.

**Fig. 3.** Macular cherry-red spot and optic disk paleness in the ocular fundus.

**Fig. 4.** Thin-layer chromatogram of urinary oligosaccharides from a patient with type II sialidosis (lane 1), our patient (lane 2) and the lactose standard (lane 3). The two major abnormal sialyloligosaccharide bands are indicated by arrows.
Fig. 5. Skin biopsy: dermal fibroblast containing dense granulofibrillar inclusions (arrows) among mitochondria (M). Magnification $\times 21,000$.

brainstem cisterns and ventricles was also observed (fig. 2). Ocular examination revealed a reduced visual acuity in both eyes for counting fingers, the fundi showed bilateral classic macular cherry-red spots with a greyish perimacular halo and optic disc paleness (fig. 3).

**Lysosomal Enzyme Determination in Fibroblasts and Urine Analysis**

Skin fibroblasts were cultured in Eagle’s minimum essential medium + fetal calf serum + penicillin-streptomycin. Lysosomal enzyme activities were determined fluorimetrically according to Galjard [7]. Sialidase activity was determined with 4-methylumbelliferyl-$\alpha$-N-acetyl neuraminic acid as the substrate. Urine oligosaccharide analysis was performed according to Blom et al. [8]. Urine was desalted using an anion and cation exchange resin.

**Skin Biopsy**

For electron-microscopic examination, the skin biopsy was fixed in 4% glutaraldehyde and postfixed in 2% osmium tetroxide, dehydrated in graded alcohols and embedded in Araldite (Fluka, Buchs, Switzerland). Ultrathin sections were stained with 2% uranyl acetate and lead citrate and examined with a Philips CM 10 electron microscope at 60 kV.

**Table 1. Enzyme activities in fibroblasts**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Patient</th>
<th>Control range</th>
</tr>
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<tbody>
<tr>
<td>Neuraminidase</td>
<td>2.2</td>
<td>30–100</td>
</tr>
<tr>
<td>$\beta$-Galactosidase</td>
<td>1,400</td>
<td>400–1,600</td>
</tr>
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Enzyme activities are expressed in nmol/h/mg protein.

**Results**

Lysosomal enzyme determination in fibroblasts of the patient showed a profound deficiency of neuraminidase and normal activity of $\beta$-galactosidase (table 1).

The results of the thin-layer chromatogram of the patient’s urine in comparison to urine of a patient with type II sialidosis are shown in figure 4. Two abnormal oli-
gosaccharide bands occur in both patients’ urine; however, the concentration in our patient’s urine is much lower than that in the urine of the sialidosis type II patient.

An electron-microscopic study of the patient’s skin showed the presence of two types of membrane-bound inclusions. Granular inclusions (diameter: 0.5 µm) were observed in several fibroblasts, in Schwann cells of myelinated fibres (diameter: 0.3 µm) and in some vascular smooth muscle cells. Pleomorphic inclusions were found in Schwann cells of myelinated fibres lying between smooth muscle fibres (fig. 5, 6).

**Discussion**

An Italian patient with unusually mild type I sialidosis was biochemically diagnosed. Although neuraminidase was clearly deficient, a residual activity was present. This is consistent with a relatively low amount of abnormal urinary oligosaccharides. This patient is, to our knowledge, the first case followed over a long period of time, showing that the disease may have a long course.

Clinically, the syndrome was described by Guazzi et al. in 1968 [9, 10]. Neuraminidase deficiency together with excretion of sialyloligosaccharides in urine were subsequently demonstrated in few patients with similar features [11–15]. Since 1979, about 15 other confirmed patients have been described [16–24]. This syndrome is now generally referred to type I sialidosis. The age of onset is generally in the second decade. The age of death has only been reported in 2 patients who died at the age of 32 [9] and 22 years [18], respectively.

An unusual feature in our patient was the late appearance of the macular cherry-red spot. The patient presented a progressive decrease in visual acuity beginning at the age of 23 years, and on examination corneal opacities and

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**Fig. 6.** Skin biopsy: membrane-bound inclusions composed of heterogeneous aggregates of mixed granulolamellar structures and lipid droplets in a Schwann cell surrounding unmyelinated axons (A) close to smooth muscle fibres. Magnification ×14,700.
an irregular macular reflex were observed. Ocular examination was not performed after the age of 27 years. Typical macular red spots and optic disc paleness were present when we examined the patient at the age of 40 years. The cherry-red spot reflects accumulation of storage material in the retinal ganglion cells, while the optic atrophy may be due both to storage materials and death of ganglion cells. In our patient, storage materials and loss of ganglion cells might have developed slowly, probably as the result of a residual turnover of sialylated compounds.

A brain CT scan performed at 21 years showed a slight enlargement of the fourth ventricle and cisterna ambiens. Cerebellar atrophy is commonly reported in the brain CT scan of patients with type I sialidosis, although the CT scan can be normal even in patients with neurological impairment [15, 18]. The MRI performed after 19 years showed, together with a severe atrophy of cerebellar hemispheres and of the pontine region, a severe involvement of the cerebral hemispheres and of the corpus callosum which appeared also atrophic. These neuroradiological findings, although not specific, point out, according to the reported pathological findings [25], a prominent involvement of the cerebellar cortex, especially during the first years of the disease’s course, and also show the progressive wide spreading of the pathological process to cerebral neurons and their neurites.

The absence of dysmorphism, vacuolated lymphocytes, storage cells in bone marrow, osseous lesions and a milder course distinguish type I sialidosis from type II. Recently, the identification of 4 mutations in patients with type II sialidosis has been reported [26, 27]. For sialidosis type I, a mutation in only one allele of the neuraminidase gene has been found in 2 patients while the mutation in the second allele is yet unknown [27].

In conclusion, the protracted course of the disease of our patient, together with the late appearance of cherry-red spots and some neuroradiological observations, extend the clinical spectrum of type I sialidosis.

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