Type II sialidosis: review of the clinical spectrum and identification of a new splicing defect with chitotriosidase assessment in two patients

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LETTER TO THE EDITORS

Type II sialidosis: review of the clinical spectrum and identification of a new splicing defect with chitotriosidase assessment in two patients

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Abstract Sialidosis is a lysosomal storage disease caused by the deficiency of alpha-*N*-acetyl neuraminidase-1 (NEU1). Sialidosis is classified into two main clinical variants: Type I, the milder form of the disease, and Type II, which can in turn be subdivided into three forms: congenital, infantile and juvenile. We report herein the clinical, biochemical and molecular characterisation of two patients with Type II sialidosis exhibiting the congenital (P1) and infantile forms (P2). We also review clinical data on the rare Type II forms of sialidosis in the hope of improving understanding of the disorder and facilitating its diagnosis. The genetic characterization of the two patients showed one known [c. 679G > A (p.G227R)] *NEU1* missense mutation (detected in P2), and the new c.807 + 1G > A splicing defect (detected in P1), a genetic lesion that is extremely rare in this disease. Interestingly, P2 presented an extremely elevated level of chitotriosidase in plasma. This is the first pathological detection of chitotriosidase in sialidosis patients.

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Introduction

Patients with Type II sialidosis develop progressive mucopolysaccharidosis-like features, including coarse facies, visceromegaly, dysostosis multiplex, and severe mental retardation.

To our knowledge, only one study mentions the assay of chitotriosidase in one sialidosis plasma sample that did not exhibit an increase in enzyme activity [9]. Chitotriosidase is markedly secreted by activated macrophages in various conditions involving inflammatory processes, atherosclerosis and hematological disorders. Increases in this enzyme's activity have also been detected in plasma specimens from some patients with lysosomal storage disorders [9, 10, 17].

Patients

The main clinical manifestations of P1 and P2 and of previously reported patients with Type II sialidosis are reported in Tables 1 and 2. The infantile and the juvenile phenotype of Type II sialidosis are presented together in Table 2.

P1 and P2 presented normal beta-galactosidase activity, and, respectively no residual NEU1 activity and 0.31 nmol/

Table 1 Main clinical features of the previously reported Type II sialidosis patients affected by the congenital form

Reference	[14]	[23]	[6]	[2]	[8]	[12]	[34]	[30]	[24]	[16]		[18]	[27]
Sex	F	F	M	F	F	2 M, 2 F	M	–	–	F	M, F	F	F
Hydrops	–	+	+	+	+	+	+	+	+	+	+	–	+
Ascites	+	+	+	+	+	+	+	+	+	–	–	+	+
Oedema	+	–	+	+	+	+	+	–	no	–	–	no	+
Course facies	+		+	+	+	–	–	+	no	–	–	+	no
Spleen/liver megaly	+	+	+	+	+	–	+	+	–	–	–	+	+
Inguinal ernia	–	–	–	–	–	–	–	–	–	–	–	+	–
Telangiectases	–	–	–	–	–	+	–	–	–	–	–	–	–
Petechie	–	–	–	–	–	–	–	+	–	–	–	–	–
Hypotonia	–	–	–	–	–	–	–	–	–	–	–	–	–
Psychomotor delay	–	–	–	–	–	–	–	–	+	–	–	+	–
Dysostosis multiplex	+	–	–	–	+	–	no	–	–	–	–	+	–
Eyes	–	–	–	–	cc	–	no	–	crs	–	–	–	–
Cardiac anomalies	+	–	–	–	–	–	–	+	–	–	–	+	–
Respiratory Infection/distress	–	–	–	+	–	–	–	–	–	–	–	–	+
Seizures/Myoclonus	–	–	–	–	–	+	–	–	–	–	–	–	+
Renal involvement	–	–	–	+	–	–	–	–	–	–	–	–	
Exitus	26 months	4 months	3 days	6 months	–	Stillborn, 1 months, 3 months, alive 3 months	56 days	–	28 days	82 days	2years	Alive (2 months)	5 months

Reference	[20]	[28]	[29]	[4]	[32]		[5]	[22]	[11]	[25]	[21]		[15]	P1
Sex	M	M	M	M	M	M	F	F	M	F	–	–	–	F
Hydrops	+	+	+	+	+	+	+	+	+	+	–	–	+	–
Ascites	+	–	+	+	+	+	+	+	+	–	–	–	+	–
Oedema	–	no	+	+	+	+	+	+	+	–	–	–	+	–
Course facies	+	+	–	–	–	–	+	–	–	+	–	–	–	+
Spleen/liver megaly	+	+	+	+	–	–	+	–	+	+	–	–	+	+
Inguinal ernia	+	+	–	no	–	–	–	–	–	–	–	–	–	–
Telangiectases	–	–	–	+	–	–	+	–	–	–	–	–	–	+
Petechie	–	–	–	–	–	–	+	–	–	–	–	–	–	+
Hypotonia	–	–	–	+	–	–	+	–	–	+	–	–	–	+
Psychomotor delay	–	–	–	–	–	–	+	–	–	+	–	–	–	+
Dysostosis multiplex	no	–	–	no	–	–	+	–	–	+	–	–	no	+
Eyes	no	cc	–	no	–	–	yr	–	–	–	–	–	–	–
Cardiac anomalies	–	–	–	+	–	–	+	–	–	+	–	–	–	+
Respiratory Infection/distress	–	–	+	+	–	–	+	–	–	–	–	–	–	–
Seizures/Myoclonus	–	–	–	–	–	–	–	+	–	–	–	–	–	–
Renal involvement	+	–	–	–	–	–	+	–	–	–	–	–	–	+
Exitus	27 days	28 days	2 months	82 days	–	–	19 months	–	27 days	20 months	3 months	2 months	Alive (3 months)	1 year

Cases reported in the same column are brothers; for reference [16] data are referred to the female patient of the twins

+ Presence of the symptom, – not reported data, *no* absence of the symptom, *crs* cherry red spot, *cc* corneal clouding, *yr* yellow retina

Table 2 Main clinical features of the previously reported Type II sialidosis patients affected by the infantile/juvenile forms of the disease

Reference	[33]	[14]		[13]		[19]	[35]	[3]		[1]	[25]		[21]		[26]	[7]	P2
Sex	M	F	F	M	F	F	M	F	M	F	M	M	–	–	F	M	M
Age at onset	<1 year	<1 year	Birth	5 months	–	<1year	18 months	12 years	Birth	6 months	<1 year	16 months	–	–	<1 year	–	1 year
Course facies	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+
Spleen/liver megaly	–	+	+	+	+	+	no	no	+	–	+	+	+	+	+	–	–
Inguinal (I)/umbilical (U) ernia	I	U	U	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hearing loss	+	–	+	+	+	–	+	+	–	+	+	+	–	–	–	–	+
Hypotonia	–	–	+	–	–	+	+	–	–	+	+	+	–	–	–	–	–
Psycho motor delay	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+
Dysostosis multiplex	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+
Eyes*	v	crs	c	crs, c, cc	crs, c	crs	crs, o, n	crs	–	crs, st, n	–	–	–	–	–	–	crs, c
Cardiac anomalies	–	+	+	–	–	–	–	–	–	–	+	no	–	–	–	+	–
Respiratory distress	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ataxia	–	–	–	+	–	+	+	+	–	–	+	–	–	–	–	–	–
Renal involvement	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–
Seizures	+	+/Myoclonic jerks	–	–	–	Myo clonus	+/Myoclonic jerks	Myo clonus	–	–	Myoclonic movement	–	–	–	–	Myoclonic epilepsy	+
Age	Died (22 years)	5½	24 months	13 years	12 years	5 years	12 years	28 years	4 months	Died (30 years)	13 years	11 years	3 years	3 years	11 years	14 years	9 years

A clinical review of Type II patients published before 1979 has been reported in Lowden and O'Brien 1979

+ Presence of the symptom, – not reported data, *no* absence of the symptom, *crs* cherry red spot, *cc* corneal clouding, *o* optic atrophy, *st* strabismous, *n* nystagmous, *c* cataract, *v* visual loss

mg/h (vn = 131.5 ± 65.7) NEU1 activity, detected in fibroblasts.

P1 exhibits the congenital form of the disease with trombocytopenia and pulmonary interstitial thickening. P2 presented with psychomotor delay, congenital cataract and sensorineural hearing loss in the first year. He went on to develop dysostosis multiplex with regression of psychomotor development, cherry red spot and epilepsy in the early years of childhood. He also presented extremely elevated chitotriosidase levels (12,600 nmol/ml/h vn 25.75 ± 17), about 250 times the normal level.

Both congenital and infantile/juvenile phenotypes, present course facies, psychomotor delay, organomegaly and ocular manifestations. Clinical evidence on Type II patients reveals the distinctive features of congenital sialidosis to be hydrops, ascites, oedema, skin telangiectases and petechie, and hydrocephalus (only one case) [5]. A private and atypical sign of the longer surviving phenotype is microcephaly, found in a 12 year old patient [3].

Myoclonic seizures are well documented in Type I sialidosis [31], but it should be noted that 8/17 Type II infantile/juvenile and 3/28 patients with the congenital form exhibited epileptic seizures or myoclonus (Tables 1, 2). Renal involvement is present in only a few cases: one belonging to the hydropic form and four to the infantile/juvenile phenotypes.

Molecular analysis

Molecular analysis identified one known [c.679G > A (p.G227R)] missense mutation [16], and the new splicing transition c.807 + 1G > A. Both mutations were homozygous.

The splicing defect gives rise to at least one aberrant mRNA transcript containing the genetic sequence of intron 4. This insertion results in the premature UGA stop codon starting at position c.807 + 13.

In the proximal promoter of P2's chitotriosidase gene (*CHIT1*) no mutations or SNPs were observed.

Screening of the 24 bp duplication in exon 10 of *CHIT1* (leading to a complete but non pathological enzyme defect) showed normal PCR products in both patients.

Discussion

Clinical onset, severity of symptoms and course differ in the congenital and infantile/juvenile subgroups. Ascites and oedema are clearly related to the more severe congenital group of the disease. In longer surviving phenotypes oedema was present in only one infantile patient [26]. On the other hand some clinical manifestations such as ataxia, anorexia and hearing loss, characteristic of the late-onset Type II subgroups, are likely to become increasingly severe as patients age.

The evaluation of chitotriosidase was useful in the differential diagnosis of the disease in P2. The patient was first hospitalized after epileptic seizures at 1 year of age and was initially suspected of suffering from Gaucher disease due to the high level of plasma chitotriosidase. An increased expression of P2' s *CHIT1* was excluded by amplifying and sequencing its promoter region. Thus, plasma chitotriosidase could be a supplementary biochemical marker that might be worth investigating in such patients.

Molecular characterization of P1's *NEU1* gene showed the new allelic variant c.807 + 1G > A. To our knowledge only one additional splicing defect has been reported [22].

The known c. 679G > A (p.G227R) mutation has a relatively high occurrence and our findings support the hypothesis of an European ancestry [3].

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