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ORIGINAL ARTICLE

A possible biomarker of neurocytolysis in infantile gangliosidoses: aspartate transaminase

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Abstract

Gangliosidoses (GM1 and GM2 gangliosidosis) are rare, autosomal recessive progressive neurodegenerative lysosomal storage disorders caused by defects in the degradation of glycosphingolipids. We aimed to investigate clinical, biochemical and molecular genetic spectrum of Turkish patients with infantile gangliosidoses and examined the potential role of serum aspartate transaminase levels as a biomarker. We confirmed the diagnosis of GM1 and GM2 gangliosidosis based on clinical findings with specific enzyme and/or molecular analyses. We retrospectively reviewed serum aspartate transaminase levels of patients with other biochemical parameters. Serum aspartate transaminase level was elevated in all GM1 and GM2 gangliosidosis patients in whom the test was performed, along with normal alanine transaminase. Aspartate transaminase can be a biochemical diagnostic clue for infantile gangliosidoses. It might be a simple but important biomarker for diagnosis, follow up, prognosis and monitoring of the response for the future therapies in these patients.

Keywords GM1-gangliosidosis · Tay-Sachs disease · Sandhoff disease · Aspartate transaminase · Aspartate aminotransferase · Biomarker

Introduction

Gangliosidoses are inherited metabolic diseases of lysosomal sphingolipid catabolism and is classified into two subtypes as GM1 gangliosidosis and GM2 gangliosidosis (Tay-Sachs disease, Sandhoff disease, GM2 activator protein deficiency). β-galactosidase, β-hexosaminidase A, β-hexosaminidase A + B and GM2 activator deficiency due to *GLB1, HEXA, HEXB* and *GM2A* gene mutations are responsible for these disorders respectively. The infantile, late-infantile, juvenile and adult forms of disease are also described based on age of onset, rate of disease progression and age of death (Vanier et al. 2016). Children with early infantile GM1 gangliosidosis are typically hypotonic during the neonatal period, but developmental arrest becomes evident after 3–6 months, usually with accompanying hypotonia, feeding difficulties and failure to thrive. Dysmorphic features, puffy, edematous face, gingival hypertrophy, macroglossia, kyphoscoliosis, cherry-red spots may be present. Loss of vision with nystagmus and spasticity usually develop in the following months with rapid neurological deterioration and death during the second year of life (Vanier et al. 2016). Patients with infantile GM2 gangliosidosis commonly present with hypotonia around 4–6 months of age. A typical accompanying feature may be hyperacusis, characterized by a startle reaction to sudden sounds. Cherry-red spots are almost always present. Similar to GM1 gangliosidosis, the disease progresses with loss of developmental milestones, loss of vision, spasticity, feeding difficulties, macrocephaly and convulsions. Dementia ensues by the third year of life, commonly resulting in death due to aspiration pneumonia (Vanier et al. 2016). Brain is the main affected organ in gangliosidoses, while hepatosplenomegaly is seen in infantile GM1 gangliosidosis and rarely in infantile Sandhoff patients. Accumulation of gangliosides in the central nervous system (CNS) is associated with progressive neurodegeneration. Neuronal apoptosis, abnormal axoplasmic transport and inflammatory response secondary to massive neuronal

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lysosomal storage of gangliosides and related glycoconjugates are considered to be involved in the pathogenesis of neurodegeneration (Satoh et al. 2007). In gangliosidoses, elevated levels of aspartate transaminase (AST, aspartate aminotransferase, glutamic oxaloacetic transaminase, GOT, SGOT) in serum and AST, lactate dehydrogenase (LDH), neuron specific enolase (NSE), myelin basic protein (MBP) and sphingolipid levels including GM1, GM2, GM3 gangliosides in cerebrospinal fluid (CSF) were reported and they were considered as biomarkers of neurodegeneration in animal models (Yamato et al. 2004; Satoh et al. 2007; Bradbury et al. 2015; Osmon et al. 2016; Gray-Edwards et al. 2017a, b, 2018) and human patients (Aronson et al. 1961; Schneck et al. 1964; Lee et al. 2018).

Elevations of AST have been evaluated and reported in GM1 gangliosidosis patients and GM1 and GM2 animal models (Aronson et al. 1958-1961; Schneck et al. 1964; Yamato et al. 2004; Satoh et al. 2007; Bradbury et al. 2015; Gray-Edwards et al. 2017a, 2018; Lee et al. 2018). Elevations of AST have been also reported in other neurological disorders including Alzheimer's disease, brain insult and stroke (Bradbury et al. 2015). The increased activities of AST and LDH in CSF are thought to be due to leakage from neuronal and other CNS cells damaged by the accumulation of specific storage materials and these enzymes reflect the rate and degree of neurocytolysis (Aronson et al. 1958, 1961; Satoh et al. 2007). Because perinatal brain damage may also cause a transitory rise of AST and LDH activity (Lending et al. 1959; Schneck et al. 1964), measurement of these enzymes should be performed after six weeks of life and progressive rise of activity in serial determinations is more significant than a single enzyme determination (Schneck et al. 1964).

There are no approved treatments for gangliosidoses and prognosis is poor especially in infantile type, resulting in death before four years of age. However adeno-associated virus gene therapy was used in GM1 and GM2 animal models with some success and AST and LDH in CSF and AST in serum were used as biomarkers in these preclinical trials (McCurdy et al. 2014; Bradbury et al. 2015; Gray-Edwards et al. 2017a, 2018). Their elevations were found to correlate well with disease severity and decrements were correlated with good response to treatment (Bradbury et al. 2015; Gray-Edwards et al. 2017a, 2018). In the present study, we retrospectively reviewed serum AST and LDH levels of our patients with infantile gangliosidoses to investigate a potential serum biomarker of neurocytolysis.

Material and methods

Fifteen patients from fourteen families with a diagnosis of infantile GM1 or GM2 gangliosidosis by clinical, enzymatic and/or molecular analyses were included in the study. Serum AST and other routine biochemical parameters including creatine kinase (CK) and LDH levels of patients were examined retrospectively. CK was evaluated to rule out damage to skeletal muscles. Serum AST was determined by the methodology recommended by the International Federation of Clinical Chemistry (IFCC) and measured using an automated serum biochemical analyzer (BECKMAN COULTER AU 5800, USA). The number of tests replicated for AST was 1–19 in 13 patients (in two patients AST was not measured) and for LDH was measured twice in one patient. Line graphs were plotted by using the median values of AST level.

Enzyme analyses (β-galactosidase, β-hexosaminidase A, β-hexosaminidase A + B) were studied on leukocytes and/or plasma (**Gazi Metabolism Laboratory and ***Manchester Centre for Genomic Medicine, Willink Biochemical Genetics Laboratory). Enzyme activities were determined by spectrofluometric methods using 4-methylumbelliferyl derivatize substrats (Kresse et al. 1981; Wenger and Williams 1991). Molecular analysis of the *GLB1*, *HEXA* and *HEXB* genes were performed on genomic DNA by conventional Sanger sequencing.

Results

There were 15 patients diagnosed with infantile gangliosidosis, four of whom had infantile GM1-gangliosidosis and 11 had infantile GM2 gangliosidosis (seven Tay-Sachs disease, four Sandhoff disease) (Table 1). The median (min-max) ages of onset, admission and diagnosis were 6 (Aronson et al. 1958, 1961; Bradbury et al. 2015; Gray-Edwards et al. 2017a, b, 2018; Kodama et al. 2011), 11 (1–22) and 13 (3–24) months respectively. Male to female ratio was 8:7. Parental consanguinity rate was 11/14 (79%). Symptoms at hospital admissions, when patients' decline was so severe or noticeable that the parents brought the patients to the hospital, were delayed motor development, developmental regression, generalized weakness, irritability, seizures, dysphagia, recurrent upper respiratory tract infections and aspiration pneumonia. In physical examination, mongolian spots, hepatosplenomegaly, microcephaly, macrocephaly, developmental delay, hypotonia, hyperacusis, hyperesthesis, irritability, nystagmus, vision and hearing loss, increased deep tendon reflexes and positive Babinski signs were determined. While the symptoms were similar in both GM1 and GM2 gangliosidoses patients, mongolian spots, facial dysmorphism and hepatosplenomegaly were more prominent in GM1 gangliosidosis patients. Cherry red spot was seen in 12/15 (80%), hyperacusis in 9/15 (60%) and nystagmus in 6/15 (40%). Hepatosplenomegaly was seen in all four patients with GM1 gangliosidosis and in only one patient with Sandhoff disease. Plasma chitotriosidase level was normal in GM2 gangliosidosis (9/9 patients, not measured in two patients) and it was elevated in one GM1 gangliosidosis patient in whom

Table 1 Clinical, biochemical and molecular genetic findings of patients with infantile gangliosidosis

Patient No ($N = 15$)	Sex	Diagnosis	Enzyme levels*	Age of onset/ admission/ diagnosis/ current (month)	Consanguinity	Clinical findings	CRS/HA/ NYS	Clinical course (month)	Chitotriosidase (nmol/h/ml) (N: 0–120)	AST range (min-max) (U/L) ($N < 40$)	Mutation; Protein effect (homozygous)
1	F	GM1	11 (107.3 ± 35.8)** nmol/h/mg protein	1/8/10/18	+	Hypotonia, developmental delay, malnutrition, hepatosplenomegaly, mongolian spot	± /−	Developmental delay	513	132–148	c.562G > A;p.E188K novel
2	M	GM1	6 (100–400)*** umol/g/h	1/2/3/deceased (Lending et al. 1959)	+	Microcephaly, hypotonia, developmental delay, hepatosplenomegaly, mongolian spot	−/−/−	Deceased (Lending et al. 1959)	NA	46–74	c.1792_1801del10bp;p.S598Qfs*6
3	M	GM1	12,2 (100–400)*** umol/g/h	7/10/12/ deceased (22)	+	Hypotonia, developmental delay, hepatosplenomegaly, gingival hypertrophy	± /+	Deceased (22)	NA	184	c.569G > A;p.G190D
4	M	GM1	2,74 (100–400)*** umol/g/h	2.5/7/13/20	+	Microcephaly, hypotonia, developmental delay, hepatosplenomegaly, dysmorphic features, hearing loss, spasticity, mongolian spot, umblical hernia	−/−/−	Developmental delay	NA	79–88	c.442C > T;p.R148C
5	F	Tay-Sachs	1.04 (50–250)*** umol/l/h	5 /11/14/59	–	Hypotonia, developmental delay, malnutrition refracter seizures, dysphagia, recurrent URTI, aspiration pneumonia, PEG+	+/+/−	Developmental delay	N	82–144	NA
6	M	Tay-Sachs	0.84 (116 ± 39)** nmol/h/mg protein	6/22/24/ deceased (32)	+	Hypotonia, developmental delay, seizures	+/+/−	Deceased (32)	N	156	NA
7	F	Tay-Sachs	0.84 (116 ± 39)** nmol/h/mg protein 3 (50–250)*** umol/l/h	6/12/15/ deceased (24)	–	Hypotonia, developmental delay, seizures	+/+/−	Deceased (24)	NA	132–185	c.1096_1107del12bp;p.366_369delYGKG
8	F	Tay-Sachs	0.7 (116 ± 39)** nmol/h/mg protein	6/15/18/ deceased (45)	+	Hypotonia, developmental delay, refractory seizures	+/+/+	Deceased (45)	NA	244–261	NA
9	F	Tay-Sachs	0.97 (116 ± 39)** nmol/h/mg protein	6/11/13/ deceased (42)	+	Hypotonia, developmental delay, refractory seizures PEG+	+/+/+	Deceased (42)	N	62–212	c.1096_1107del12bp;p.366_369delYGKG
[a]10	M	Tay-Sachs	3.85 (116 ± 39)** nmol/h/mg protein	7/12/14/22	+	Hypotonia, developmental delay	+/+/−	Developmental delay	N	205–245	c.1096_1107del12bp;p.366_369delYGKG
[a]11	M	Tay-Sachs	3.66 (116 ± 39)** nmol/h/mg protein	1/1/4/10	+	Developmental delay	−/−/−	Developmental delay	N	NA	c.1096_1107del12bp;p.366_369delYGKG
12	F	Sandhoff	43 (600–3500)*** umol/l/h	6/12/15/deceased (42)	–	Hypotonia, developmental delay, malnutrition,	+/+/−	Deceased (42)	N	151	c.1287 T > A/c.1242 + 3G > T (p.Y429*;

Table 1 (continued)

Patient No (N = 15)	Sex	Diagnosis	Enzyme levels*	Age of onset/ admission/ diagnosis/ current (month)	Consanguinity	Clinical findings	CRS/HA/ NYS	Clinical course (month)	Chitotriosidase (nmol/h/ml) (N: 0–120)	AST range (min-max) (U/L) (N < 40)	Mutation; Protein effect (homozygous)
						refractory seizures, dysphagia, recurrent URTI, aspiration pneumonia					IVS10 + 3G > T) (compound heterezygous)
13	F	Sandhoff	90 (1223 ± 273)** nmol/h/mg protein	6/11/16/ deceased (38)	+	Hypotonia, developmental delay, left renal agenesis, refractory seizures, PEG+	+/+/+	Deceased (38)	N	56–158	c.1417 + 5G > A;IVS11+ 5G > A
14	M	Sandhoff	287 (1223 ± 273)** nmol/h/mg protein	6/10/11/19	+	Hypotonia, developmental delay, hepatosplenomegaly, mongolian spot	+/−/+	Developmental delay	N	NA	c.1538 T > C (p.L513P)/?
15	M	Sandhoff	220 (1223 ± 273)** nmol/h/mg protein	6/8/10/19	+	Hypotonia, developmental delay, malnutrition, macrocephaly	+/+/+	Developmental delay	N	148–150	c.171_185dupGCCCC TGCCGCTCTT

Age of admission: Age that the patients' decline was so severe or noticeable that the parents brought the patients to the hospital Current age: Age of patients at the time of writing Clinical findings: occur over multiple time points Chitotriosidase levels were measured at the time of admission *M* male, *F* female, *CRS* cherry red spots, *HA* hyperacusis, *NYS* Nystagmus, *AST* aspartate transaminase, *PEG* percutaneous endoscopic gastrostomy, *URTI* upper respiratory tract infection, ?: not found [a] sibling, +: yes, −: no, NA: not available *Enzyme levels for GM1-gangliosidosis: B-galactosidase, for Tay-Sachs disease: β-hexosaminidase A, and for Sandhoff disease: β-hexosaminidase A + B were studied. **: Gazi Metabolism Laboratory ***: Willink Laboratory

it was measured. Isolated serum AST levels were increased, varying from 46 to 184 U/L (<40) in GM1 gangliosidosis patients, 62 to 261 U/L (<40) in Tay-Sachs patients, 56 to 158 U/L (<40) in Sandhoff patients (Table 2, Figs. 1, 2, and 3). Lactate dehydrogenase (LDH) activity was measured only in one Sandhoff patient (patient no: 13) and it was elevated [LDH: 690–1326 IU/L (N: 142–297)]. Other liver function tests including ALT (alanine transaminase), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and abdominal sonography were normal. Urinalysis, kidney function tests, echocardiography, electrocardiography and CK were also normal. Two of four GM1 gangliosidosis patients died before the age of two, 4/7 Tay-Sachs patients died between 2 and 4 years of age, and 2/4 of Sandhoff patients died between 3 and 4 years of age. Molecular analyses revealed homozygous c.442C > T;p.R148C, c.562G > A;p.E188K, c.569G > A;p.G190D, c.1792_1801del10bp;p.S598Qfs*6 mutations in *GLB1* gene, homozygous c.1096-1107del12bp;p.366-369delYGKG mutations in *HEXA* gene, homozygous c.177_185dupGCCCCTGCCGCTCTT, c.1417 + 5G > A;IVS11 + 5G > A and compound heterezygous c.1287 T > A; p.Y429*/c.1242 + 3G > T;IVS10 + 3G > T, c.1538 T > C;p.L513P/? mutations in *HEXB* gene.

Discussion

Biomarker investigations in gangliosidoses as well as other lysosomal storage disorders (LSDs) are ongoing with human and animal studies. GM1 ganglioside in GM1 gangliosidosis cats and dogs and GM2 ganglioside in GM2 gangliosidosis mice in CSF were reported as potential biomarkers of neurodegeneration (Yamato et al. 2004; Satoh et al. 2007; Osmon et al. 2016; Gray-Edwards et al. 2017b). Sphingolipid levels in CSF studied with targeted lipidomics were found to be highly predictive of neurologic disease progression in GM1 cats (Gray-Edwards et al. 2017b). In that study, especially GM1 ganglioside level in CSF was determined as the most reliable and robust indicator of disease progression and GM3 ganglioside in CSF was also elevated significantly and returned to normal levels after gene therapy (Gray-Edwards et al. 2017b). Lyso-GM2 in plasma was also found to be a potential biomarker of GM2-gangliosidosis patients except in GM2 activator protein deficiency (Kodama et al. 2011). Epithelial-derived neutrophil activating protein 78 (ENA-78), monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β), tumor necrosis factor receptor 2 (TNFR2) inflammation markers in CSF were also found to be specific biomarkers for infantile gangliosidosis patients (Utz et al. 2015). Elevated levels of AST, LDH, malic dehydrogenase and fructose 1,6-diphosphate aldolase (F-1,6-DPA) in serum and CSF and decreased fructose-1-phosphate

Table 2 Serum aspartate aminotransferase ($N < 40$ U/L) levels of patients with infantile gangliosidosis

Patient No	Age (months)																																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	41	42
1GM1								132	148																														
2GM1			46	74	56																																		
3GM1														184																								
4GM1							83	88						79																									
5 T											144	130	105	112	82	106																							
6 T																					156																		
7 T												132		178							147																		
8 T												244	261																										
9 T									163						174		212		139			111	116	87	107			107	90	63						72	62	78
10 T													205	245																								
11 T																																						
12S																151																						
13S											136			129	158		117	115		75	83	74	84	97	92			84	86	94		79	58	59	59	56			
14S																																						
15S										148	150																											

GM1 GM1 gangliosidosis, *T* Tay-Sachs disease, *S* Sandhoff disease

aldolase (F-1-PA) activity in serum were reported in Tay-Sachs disease patients (Aronson et al. 1961; Schneck et al. 1964; Volk et al. 1964). The role of F-1-PA enzymatic defect in ganglioside metabolism is currently obscure (Volk et al. 1964).

AST and LDH elevations in CSF correlated well with the severity of disease in GM1 cats and dogs, Sandhoff cats, Tay-Sachs sheep models and human infantile GM1 gangliosidosis patients (Aronson et al. 1958, 1961; Satoh et al. 2007; Bradbury et al. 2015; Gray-Edwards et al. 2017a, Lee et al. 2018). Elevations of both AST and LDH activities in CSF of untreated GM1 and Sandhoff cats and Tay-Sachs sheep were significantly reduced after AAV gene therapy, suggesting their utility as indicators of efficacy in human clinical trials (Bradbury et al. 2015; Gray-Edwards et al. 2017a, 2018). CSF levels of LDH (in the absence of seizures) and AST (regardless of seizures status) were robust, were easily measured in clinical samples and correlated well with CNS disease status in untreated and treated GM1 cats (Gray-Edwards et al. 2017a). Serum AST was suggested to be a valuable marker especially if CSF samples are unavailable (Gray-Edwards et al. 2017a). CNS tissue AST and LDH activities were also found to be significantly higher in GM1 dogs and their changes showed positive correlation with age (Satoh et al. 2007). In these dogs, AST and LDH increased up to the age of seven months, after which it made a plateau (Satoh et al. 2007). Similarly in our study we also observed serum AST levels were increasing to a plateau nearly to the age of 13 month, then it decreased in spite of clinical deterioration (Table 2, Figs. 1, 2, and 3). We agree that AST level increases secondary to neuronal damage for a certain period of time, but it decreases after a plateau, but never reaches to normal levels. We hypothesise that decrement of AST levels might be secondary to severe brain atrophy after a lot of neuronal loss showing the last stage of disease, similar to decrement of AST in patients with end-stage liver cirrhosis. Therefore we should always be careful to interpret results that decrements of these biomarkers do not always mean better clinical condition. Serum LDH activity was measured and was elevated in only one Sandhoff patient. We believe that serum LDH activity would be found also high in all patients secondary to neuronal damage as it was in AST. We suggest prospective studies to show correlation between serum and CSF AST and LDH levels in these patients to verify our results. AST and LDH in the serums can be reflective of AST and LDH levels in the CSF. Various biomarkers have been proposed for the gangliosidoses as discussed previously. Among these markers, AST and LDH are much simpler to measure than other biomarkers, such as GM1 and GM2 gangliosides. In addition, measurements of AST and LDH in serum are much easier, cheaper and less invasive than CSF and CNS tissue.

We also observed elevated levels of serum AST together with a normal ALT (alanine transaminase) in all gangliosidosis patients in whom the test was performed, similar to the literature (Lee et al. 2018) (Tables 1 and 2 and Figs. 1, 2, and 3). AST in serum with infantile Tay-Sachs and infantile GM1 gangliosidosis patients (Aronson et al. 1958, 1961, Schneck et al. 1964; Lee et al. 2018) and AST in CSF with GM1 cats and dogs, Sandhoff cats and Tay-Sachs sheep models had been reported as a candidate biomarker (Satoh et al. 2007; Bradbury et al. 2015; Gray-Edwards et al. 2017a, 2018). Our study supports these published observations that elevated levels of serum AST alone may be one biomarker in gangliosidosis patients. AST is not only found in liver, but also in heart, muscle, bone, brain and other organs. AST is a ubiquitously expressed enzyme (E.C 2.6.1.1) that catalyzes the interconversion of aspartate and α-ketoglutarate to oxaloacetate and glutamate and, in the CNS,

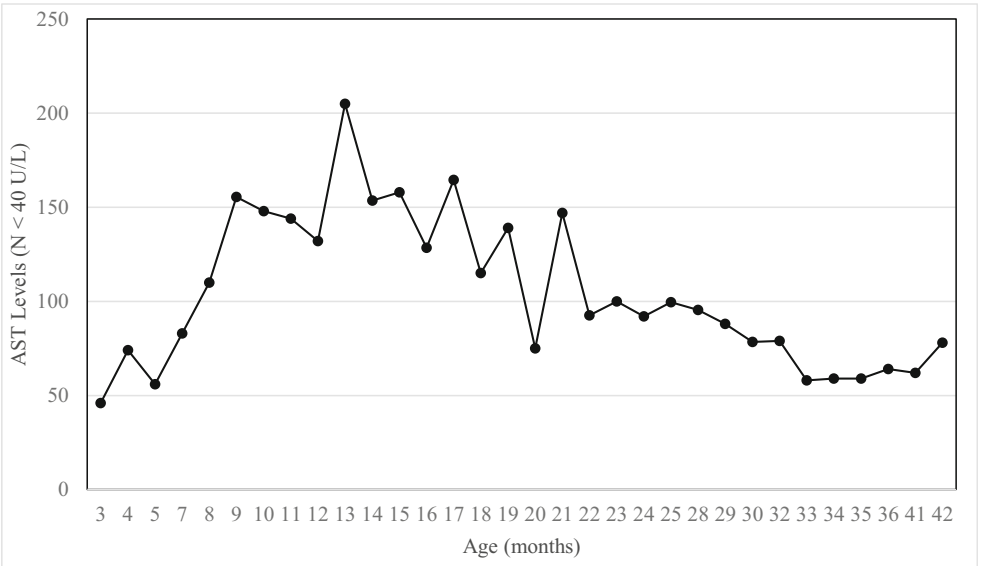

Fig. 1 Median value of serum AST levels in all gangliosidosis patients (GM1 + GM2)

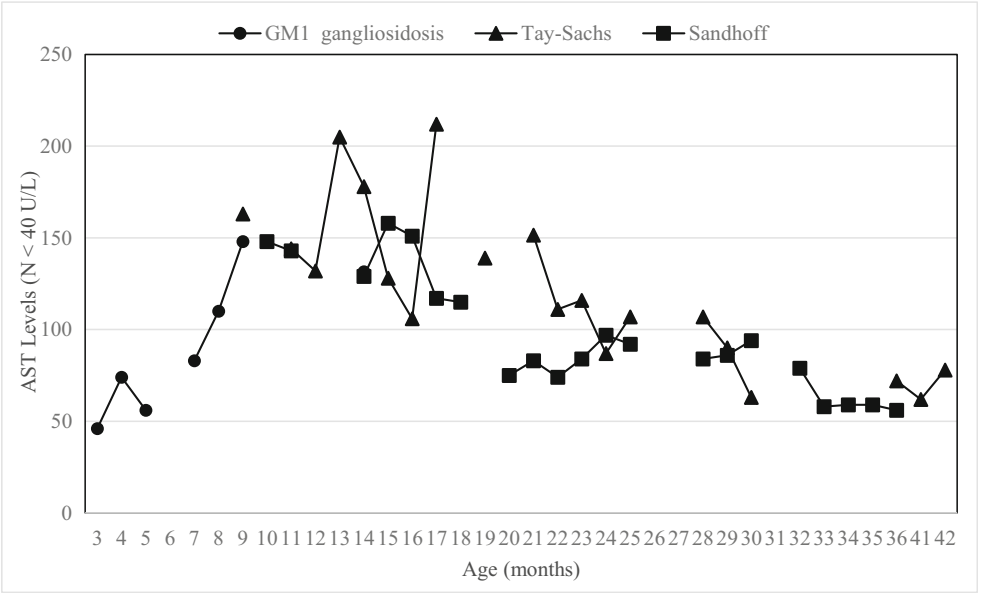

Fig. 2 Median value of serum AST levels in GM1 gangliosidosis, Tay-Sachs and Sandhoff disease patients

functions to manage levels of excitatory neurotransmitters (Bradbury et al. 2015). Similarly, LDH (EC 1.1.1.27&EC 1.1.1.28), which catalyzes the interconversion of pyruvate and lactate, is ubiquitously released from all cells after damage to the plasma membrane and is thought to reflect cytotoxicity with elevations in a wide array of neurological disorders including meningitis, prion disease, leukemia, trauma, infantile spasms, stroke and gangliosidosis (Bradbury et al. 2015). AST is located both in cytoplasm and mitochondria, while ALT is a cytosolic enzyme. In gangliosidosis with neurocytolysis, the serum level of AST can be increased due to cellular damage and apoptosis resulting from the accumulation of specific storage materials (GM1, GM2 gangliosides and related glycoconjugates) (Aronson et al. 1958; Satoh et al. 2007). Furthermore, activation of autophagy with high sensitivity to oxidative stress can lead to mitochondrial dysfunction (Takamura et al. 2008). In lysosomal storage disorders, elevated level of AST together with ALT were observed in patients with Gaucher, Niemann-Pick, Wolman disease and these elevations were found secondary to liver involvement. In our study, we support that the increased AST level arises not from other organs, but from the brain, even in GM1 gangliosidosis patients whom also had liver involvement but normal ALT. Lack of liver, kidney, heart and skeletal muscle involvement, which may be alternative sources of serum AST, was ruled out by liver and kidney function tests, coagulation tests, urinalysis, abdominal sonography, echocardiography, electrocardiography and CK.

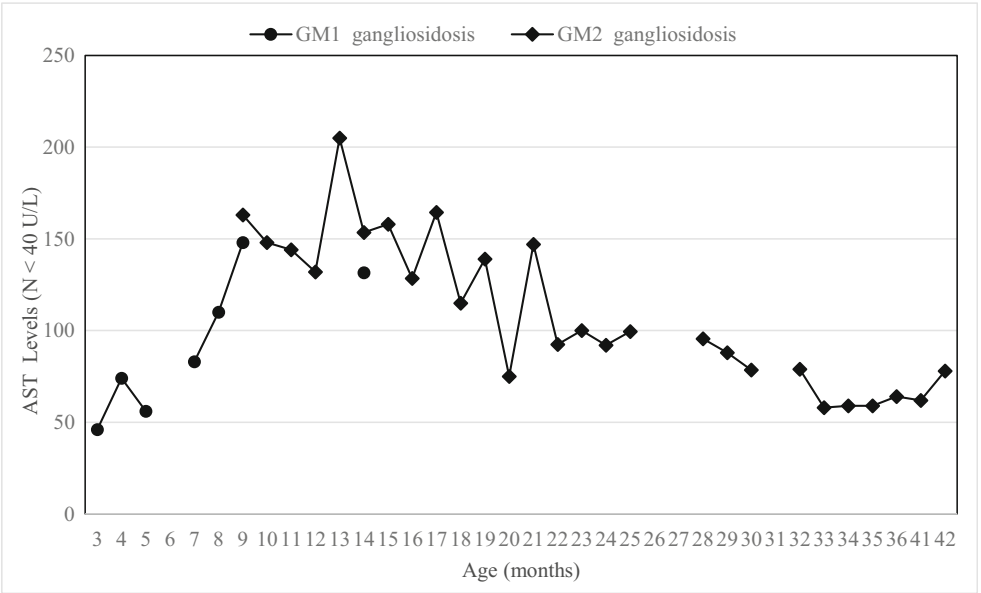

Fig. 3 Median value of serum AST levels in GM1 and GM2 (Tay-Sachs+Sandhoff) patients

Interestingly, AST elevation was not found in other lysosomal storage disorders with CNS involvement, such as remaining sphingolipidoses, oligosaccharidoses, mucopolysaccharidoses and mucolipidoses (our experience). It could be explained that disease progression was slower in these disorders than infantile GM1 and GM2 gangliosidosis. However we should review AST levels in patients with other rapidly progressive LSD such as infantile Krabbe disease, sialidosis type II, infantile sialic acid storage disorder. The lack of increase in AST in other rapidly progressive LSD would indicate that elevated AST is not related to rapid neurodegeneration, but is causally related to gangliosidoses. Lack of abnormality in other neurodegenerative lysosomal diseases may be important findings and can identify this analyte as a biomarker of neuropathology specific to the gangliosidosis disease (Satoh et al. 2007). This could be explained by neurotoxicities of gangliosides. These data support the use of a clinically relevant biomarker, AST, for application to patients with gangliosidoses.

In one of our patients, the neurologist interpreted AST elevation as a side effect of antiepileptic medication and changed the course of treatment. Although the antiepileptic medication was changed, AST elevation persisted. Therefore, it was more likely that the elevation was not related to antiepileptic medication, but it was probably a biochemical feature of infantile gangliosidoses associated with disease progression. It is also known that AST levels were unaffected by seizure activity (Gray-Edwards et al. 2017a). Therefore this knowledge is important for the neurologist to regulate antiepileptic drugs for seizures in these patients.

Although c.1096-1107del12bp;p.366-369delYGKG mutation was seen as a common variant in Tay-Sachs patients, mutation spectrum in GM1 gangliosidosis and Sandhoff patients was varied (Table 1). Prognosis is poor in infantile gangliosidosis. Most patients died before four years of age secondary to pneumonia and/or respiratory failure.

Elevated level of AST alone is not a specific biomarker, but its specificity can be increased with other clinical findings suggesting gangliosidosis such as developmental delay, hypotonia, hepatosplenomegaly, hyperacusis, cherry red spots. Serum isolated AST activity might be a simple but important biomarker to show neurocytolysis, neurodegeneration of disease progression in gangliosidosis patients. Further studies are necessary to support this hypothesis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the Medical Ethics Committee of Kecioren Training and Research Hospital.

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