INTERNAL MEDICINE

□ CASE REPORT □

Clinical and Serial MRI Findings of a Sialidosis Type I Patient with a Novel Missense Mutation in the *NEU1* Gene

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Abstract

The case of a Japanese sialidosis type I patient with a novel *NEU1* gene mutation is described. The patient developed an unsteady gait at age 14 and was referred to our hospital at age 16. On admission, subnormal intelligence, dysarthria, myoclonus, intentional tremors, limb and gait ataxia, hyperreflexia and macular cherry-red spots were observed. An enzymological analysis revealed a primary deficiency of neuraminidase. An *NEU1* gene analysis identified two heterozygous missense mutations: p.P80L and p.D135N. The p.D135N mutation is a novel mutation that is considered to be associated with the mild clinical phenotype of sialidosis. Serial brain MRI showed diffuse brain atrophy progressing rapidly over the 41-month observation period.

Key words: sialidosis, neuraminidase, ataxia, cherry-red spot, myoclonus, magnetic resonance imaging

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Introduction

Sialidosis (MIM# 256550) is an autosomal recessive lysosomal storage disease (1) caused by mutations in the *NEU1* gene encoding the enzyme lysosomal sialidase (neuraminidase, EC 3.2.1.18) (2-4), which leads to decreased enzymatic activity and accumulation of sialyloligosaccharides in tissues. Sialidosis is divided into two main clinical variants with different ages of onset and severity. Sialidosis type I, also known as "cherry-red spot myoclonus syndrome," is a relatively mild form of the disease with a late onset. Patients usually develop gait abnormalities, progressive impaired vision, bilateral macular cherry-red spots, myoclonus, ataxia and seizures in the second or third decade of life (1, 5-7). Sialidosis type II is the early-onset form and is associated with macular cherry-red spots, the Hurler-like phenotype, dysostosis multiplex, short stature, developmental delays, mental retardation and hepatosplenomegaly (1, 8, 9). The age of onset and severity of the clinical manifestations are correlated with *NEU1* mutations (10, 11) and the level of residual neuraminidase activity (10, 12, 13), indicating the existence of considerable genotype-phenotype correlation in this disease. To date, more than 40 mutations within the *NEU1* gene have been identified in patients with sialidosis type I or type II (2, 3, 10-24).

We herein report the clinicopathological, neuroradiological, enzymological and molecular biological findings of a Japanese sialidosis type I patient with a novel missense mutation in the *NEU1* gene.

Case Report

The patient, a 17-year-old Japanese young man, was the second child of non-consanguineous healthy parents and had a healthy sibling. He was born at term after a normal pregnancy with a birth weight of 3,550 g (Apgar scores: 9 at 1

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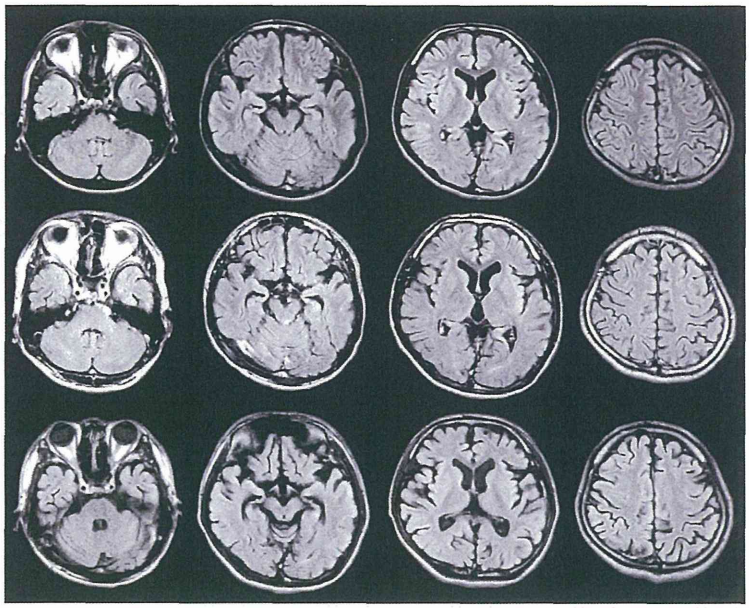

Figure 1. Serial brain MRI of the patient (FLAIR image, axial view). A (top row), B (middle row) and C (bottom row) show MRI findings obtained at 14 years and five months, 16 years and one month and 17 years and 10 months of age. Diffuse brain atrophy became more evident with age. Brain atrophy was more obvious in the inferior parts of the temporal lobe, cerebellum and brainstem region.

minute and 10 at 5 minutes). He showed normal development up to the age of 14 when he noticed an unsteady gait and frequent falls precipitated by sudden movements. He was admitted to a local hospital where he was suspected of having familial paroxysmal kinesigenic dyskinesia. At that time, mild enlargement of the lateral ventricles was detected on brain magnetic resonance imaging (MRI) (Fig. 1A). The patient was treated with carbamazepine, which did not improve his symptoms. At age 15, he noticed frequent jerky involuntary movements when walking, writing and eating and was admitted to another local hospital. On admission, dysarthria, action myoclonus, intentional tremors, cerebellar ataxia and hyperreflexia were observed. His intelligence was assessed using the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III), which revealed the following results: Full Scale IQ: 86, Verbal IQ: 97, Performance IQ: 76, Verbal Comprehension Index: 97, Perceptual Organization Index: 79, Working Memory Index: 91 and Processing Speed Index: 66. Brain MRI showed mild diffuse brain atrophy, including the cerebral hemispheres, cerebellum and brainstem (Fig. 1B). Clonazepam reduced the myoclonus; however, the patient's unsteady gait gradually deteriorated. He was suspected of having hereditary spinocerebellar ataxia and referred to our hospital at the age of 16 years.

On admission, the findings of a general examination of the patient were unremarkable. He was fully conscious, although his intelligence was subnormal (Full Scale IQ: 80, Verbal IQ: 97, Performance IQ: 64, Verbal Comprehension Index: 109, Perceptual Organization Index: 70, Working Memory Index: 69 and Processing Speed Index: 63 on WAIS-III). He had slurred and scanning speech; however, there were no abnormal findings in the cranial nerves. The muscles in the extremities were generally hypotonic, although their strength was normal and without atrophy. Intention tremors, action myoclonus and limb and gait ataxia were present. The tendon reflexes were increased without laterality. Babinski and Chaddock signs were negative on both sides. An ophthalmological examination demonstrated bilateral macular cherry-red spots (Fig. 2), although the patient's visual acuity and visual field were both normal.

The findings of routine blood examinations, cerebrospinal fluid, chest roentgenography, electrocardiography, echocardiography, electroencephalography and nerve conduction studies were normal. The somatosensory evoked potential (SEP) evoked by right median nerve stimulation showed a giant cortical response. The visual evoked potential (VEP) showed no response following pattern-reversal visual stimulation in both eyes. Brain MRI revealed moderate diffuse brain atrophy (Fig. 1C), which was more evident in comparison with that observed on the patient's previous MRIs (Fig. 1A, B). MRI of the spinal cord was normal. N-Isopropyl-(iodine-123) *p*-iodoamphetamine (^{123}I-IMP) single-photon emission computed tomography (SPECT) showed slightly decreased uptake in the right occipital and bilateral frontotemporal lobes. An electron microscopic study of a rectal mucosa biopsy showed numerous lamellar storage bodies in the ganglion cells of Meissner's plexus (Fig. 3).

The skin fibroblast neuraminidase activity was significantly decreased (0 nmol/h/mg protein) and other lysosomal enzyme activities, including those of α-galactosidase, β-galactosidase, α-glucosidase, β-glucosidase, β-hexosaminidase, β-hexosaminidase A, α-mannosidase, α-

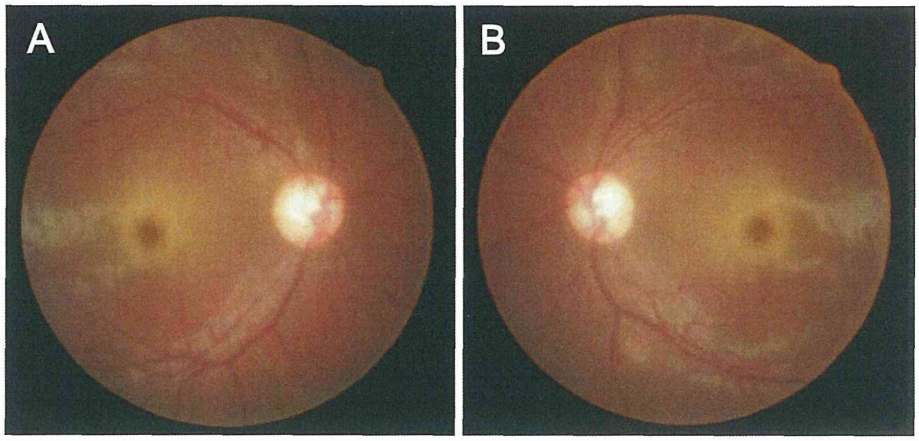

Figure 2. **Color fundus photographs of the right (A) and left (B) eyes demonstrating the classic appearance of a cherry-red spot in the maculae.**

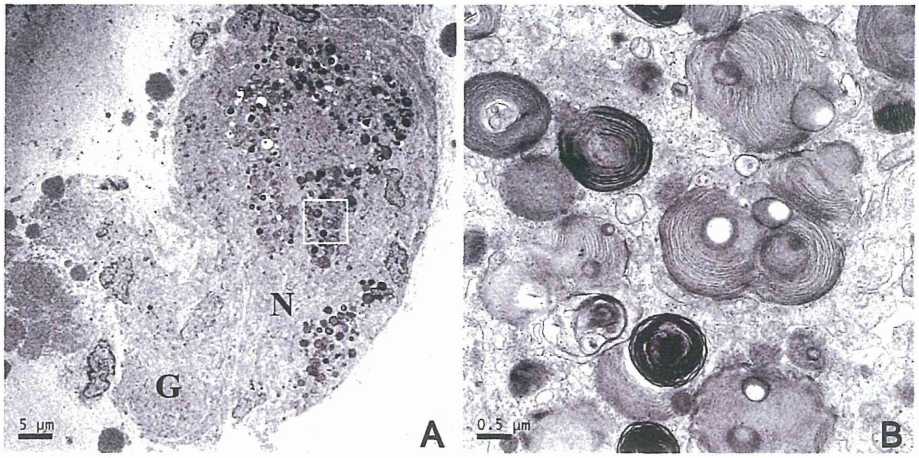

Figure 3. **An electron microscopic study of a rectal mucosa biopsy. (A) Rectal ganglion cells (N) of Meissner's plexus contained many small electron-dense inclusions. The glia cells (G) had a normal appearance. Bar = 5 μm. (B) A high-power view of the *rectangle* in A. Electron-dense inclusions were composed of osmiophilic lamellar structures lined by a unit membrane. Bar = 0.5 μm.**

fucosidase, β-glucuronidase and arylsulfatase A, were normal, which was compatible with a diagnosis of sialidosis (Table 1).

As the clinical findings and results of an enzymological analysis of the patient were suggestive of sialidosis type I, a genetic analysis of this disorder was performed with informed consent. DNA was extracted from peripheral leukocytes obtained from the patient according to the standard protocol. All 6 exons and the flanking intronic sequences of the *NEU1* gene were amplified using polymerase chain reaction (PCR). The primer sequences and PCR conditions are summarized in Table 2. A direct sequence analysis of the PCR-amplified DNA identified two heterozygous missense mutations, c.239C>T and c.403G>A (Fig. 4), which resulted in amino acid alterations of p.P80L and p.D135N, respectively. Although the *NEU1* genes of the parents were not analyzed, the results suggested that the patient was compound heterozygous for p.P80L and p.D135N. The c.239C>T (p.P80L) mutation has been reported previously in a Japanese sialidosis type II patient (12). On the other hand, the c.403G>A (p.D135N) mutation has not been previously described (HGMD Professional 2011.3, Human Gene Mutation Database, Biobase, Beverly, MA, USA and SNPs reported in the database (dbSNP) of the National Center for Biotechnology information (NCBI) (http://www.ncbi.nlm.nih.gov/SNP/)). The possible impact of a novel p.D135N mutation on the structure and function of neuraminidase was assessed using a bioinformatics tool, Polymorphism Phenotyping-2 (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/) (25), and was predicted to most likely be damaging (score: 0.991; sensitivity: 0.45, specificity: 0.97).

Discussion

Lysosomal neuraminidase requires carboxypeptidase protective protein/cathepsin A (PPCA, EC 3.4.16.1) for intracellular transport and lysosomal activation (26). Human lysosomal neuraminidase is deficient in two genetic disorders: sialidosis (MIM# 256550), caused by a mutation in the *NEU1* gene (1-4), and galactosidosis (MIM# 256540), in

Table 1. Results of Skin Fibroblast Lysosomal Enzyme Activities

Lysosomal enzyme	Present patient* (nmol/h/mg protein)	Normal control* (n=1)	Normal controls** (n=25, mean ± SD)
Neuraminidase	0.0	176.1	25.0 ± 17.0
α-galactosidase	66.4	143.9	29.6 ± 17.6
β-galactosidase	780.8	1,333.6	401 ± 184.8
α-glucosidase	118.6	264.1	50.6 ± 32.0
β-glucosidase	249.6	265.4	84.7 ± 30.5
β-hexosaminidase	9,017.8	17,060.9	4,678 ± 2,246
β-hexosaminidase A	1,458.7	2,690.1	629 ± 450
α-mannosidase	325.4	485.3	48.7 ± 27.8
α-fucosidase	166.8	332.5	64.6 ± 40.7
β-glucuronidase	51.5	142.9	19.3 ± 12.1
Arylsulfatase A	387.9	526.0	265.7 ± 129.5

* Lysosomal enzyme activities of the patient and a control were analyzed at the same time to rule out technical error. ** Lysosomal enzyme activities were analyzed previously. */** Lysosomal enzyme activities depend on condition of fibroblast, resulting in variation in enzyme activity levels among controls.

Table 2. Sequences of PCR Primers, PCR Product Size, and PCR Annealing Temperatures (T_A) Used for Analysis of the *NEU1* Gene

	Primer sequence 5'→3'	PCR product size (bp)	T_A (°C)
Exon 1F	gcttaagggtgacatctgcgcttt	373	60
Exon 1R	tgggagaaagaaaagggtcctgtc		
Exon 2F	aactccccttcgtgttcctctttc	443	60
Exon 2R	caaccaaccctctaagttcccctatc		
Exon 3F	ctagcagaaggtgggaaattaacgg	427	60
Exon 3R	gaaaggagtccatttgggggtatc		
Exon 4F	atttgggaagtggtgggttctctg	500	60
Exon 4R	agtggtagttgttctggtttcggg		
Exon 5F	agatgttccctacccatttgaccc	525	60
Exon 5R	catgaggtaccattgctgaagctc		
Exon 6F	cattgtcttcttctccaacccagc	514	60
Exon 6R	gatttccctggtaaagggaaggtg		

PCR primers complementary to intronic sequences flanking each of the 6 exons were designed based on the published genomic sequence of the *NEU1* gene (NCBI Reference Sequence: NG_008201.1).

which the loss of neuraminidase activity is secondary to a deficiency of PPCA (2). An enzymological analysis of our patient revealed a primary neuraminidase deficit with intact β-galactosidase activity. In addition, a molecular genetic analysis of the *NEU1* gene revealed that this patient was compound heterozygous for the p.P80L and p.D135N mutations, thus confirming the diagnosis of sialidosis.

The c.239C>T (p.P80L) mutation has been previously reported in a Japanese patient with severe congenital sialidosis type II (12). The P80 residue is situated in a conserved FRIP motif that is located at the N-terminus of the first strand of the first β-sheet unit. The side chain of the P80 residue is adjacent to the active site residue R78, as well as to Y370 and E394, which are located in the first strand of the sixth β-sheet unit in the wild-type neuraminidase protein. The amino acid substitution of P80 to L causes conformational changes in the main chain that affect the position of the active site residues R78, Y370 and E394 (12). In addition, a transient expression study of lysosomal neuraminidase cDNA revealed that p.P80L proteins do not show enzymatic activity and do not exhibit the typical lysosomal distribution in cultured cells, compatible with the severe congenital phenotype (12). On the other hand, c.403G>A (p.D135N) is a novel missense mutation. The D135 residue is one of the active sites of human lysosomal neuraminidase (4, 12), and amino acid substitution of D135 to N was predicted to alter the structure and function of the enzyme using the bioinformatics tool, PolyPhen-2. Based on the clinical findings of our patient and the biological properties of the second mutation (p.P80L), the novel p.D135N mutation was considered to be associated with a relatively mild clinical phenotype of sialidosis (sialidosis type I).

Diffuse brain atrophy is commonly observed in the advanced stage of sialidosis type I; however, the results of neuroradiological imaging can be normal on the first examination in affected patients (19, 20, 27-29). There have been very few studies regarding long-term changes in the findings of neuroimaging (20, 29), and it is largely unknown how rapidly brain atrophy progresses in patients with sialidosis type I. Chen et al. (19) reported the results of a long-term follow-up study of sialidosis type I siblings homozygous for the p.S182G missense mutation. The ages at onset in these patients were 14 and 17 years. The brain MRI findings of the younger brother remained normal even 18 years after onset, while those of the older sister showed mild cerebellar atrophy 11 years after onset. Palmeri et al. (29) reported the case of a 40-year-old woman who developed sialidosis type I at 17 years of age. A brain computed tomography (CT) scan of the patient performed at 21 years of age showed slight enlargement of the fourth ventricle and cisterna ambiens, whereas severe atrophy of the cerebellum, pontine region, cerebral hemispheres and corpus callosum were observed on MRI at the age of 40. Pathologically, cytoplasmic accumulation of sialyloligosaccharides has been observed in many neurons in the central nervous systems of sialidosis

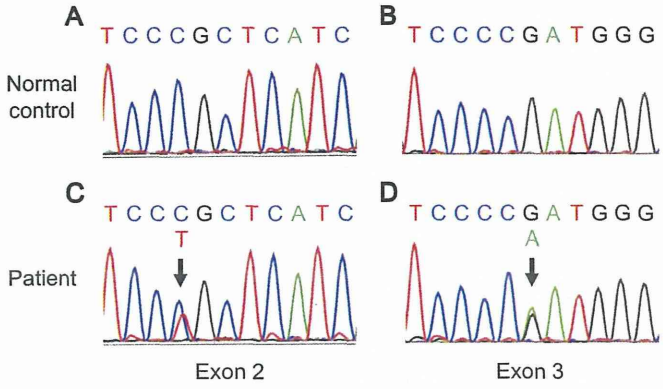

Figure 4. Direct nucleotide sequencing of the PCR-amplified *NEU1* gene DNA of a control (A, B) and the patient (C, D). The vertical arrow indicates nucleotide 239 (exon 2), where a C→T transversion (c.239C>T) resulted in an amino acid substitution, p.P80L (A, C). The arrow head indicates nucleotide 403 (exon 3), where a G→A transversion (c.403G>A) resulted in an amino acid substitution, p.D135N (B, D). The patient was compound heterozygous for the p.P80L and p.D135N mutations.

type I patients (30, 31). However, neuronal loss in these nuclei is not frequent despite massive accumulation of sialyloligosaccharides even 15 years after the onset of the disease (31), which may explain why the results of neuroradiological imaging can remain normal for a considerable period of time in sialidosis type I patients. In contrast to the findings of previous reports (19, 20), mild dilatation of the lateral ventricles was observed at the onset of disease in our patient (Fig. 1A), and his brain atrophy progressed rapidly over the 41-month observation period (Fig. 1B, C). Although the pathological mechanisms underlying this phenomenon remain to be elucidated, our observations demonstrate that brain atrophy can progress rapidly, even in the early stage of sialidosis type I.

In our patient, VEP showed no response in either eye, although the patient's visual acuity and visual field were normal. Lai et al. (20) reported that, although only four of 17 (23.5%) sialidosis type I patients initially complained of visual disturbance, 16 (94.1%) showed abnormal findings on VEP, suggesting that VEP can be a valuable neurophysiological test in the diagnosis of patients with sialidosis type I who do not present with the typical manifestations of the disease.

The authors state that they have no Conflict of Interest (COI).

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薬剤の臨床

日本人Gaucher病（Ⅰ型，Ⅱ型およびⅢ型）患者に対するセレザイム®の8年間の製造販売後調査結果による有効性と安全性の検討

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Key words
イミグルセラーゼ（遺伝子組換え）
酵素補充療法
日本人Gaucher病
有効性
安全性

要旨

Gaucher病酵素補充療法製剤イミグルセラーゼ（遺伝子組換え）〔セレザイム®〕による治療を受けた日本人Gaucher病全病型の患者を対象に実施された製造販売後調査におけるセレザイム®の有効性と安全性について検討した．調査期間中，ヘモグロビン値，血小板数，アンジオテンシン変換酵素値，酸性ホスファターゼ値および肝・脾臓容積は改善し，また，良好な忍容性が確認された．セレザイム®の効果および副作用は欧米人Gaucher病Ⅰ型患者での報告と類似しており，セレザイム®は日本人Gaucher病においても有効かつ安全性が高い治療法であると結論された．

はじめに

1．疾患概要

Gaucher病は，先天性脂質代謝異常症の一つであり，常染色体劣性遺伝形式をとる遺伝性疾患である．糖脂質を分解するライソゾーム酵素の1種であるグルコセレブロシダーゼの活性低下により，糖脂質であるグルコセレブロシドがマクロファージに蓄積し，肝脾腫や貧血，出血傾向，骨痛，骨折などの重篤な全身症状をひきおこす疾患である．神経症状の有無と重症度によりⅠ，ⅡおよびⅢ型の三つの病型に分類される．

Ⅰ型（慢性非神経型）は，神経症状を伴わない病型で，肝脾腫，貧血，骨症状を主徴とする．発症年齢，骨合併症や肝脾腫の程度などの点において臨床的異質性が顕著な病型である．Ⅱ型（急性神経型）は，乳児期に発症し，肝脾腫に加え，けいれん，後弓反張，喉頭けいれんなどの神経症状を呈し，急速に退行し，2歳頃までに死亡する予後不良の病型である．Ⅲ型（亜急性神経型）は，肝脾腫に加え，神経症状を伴うが，その発症はⅡ型に比べ遅く，また神経症状の程度も軽度で緩徐な病型である．

日本人Gaucher病の遺伝子変異分布は，欧米人，とくにユダヤ人のそれと大きく異なり，その

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臨床表現型も異なる．すなわち，ユダヤ人Gaucher病Ⅰ型は慢性に経過し，軽症である傾向があるのに対し，日本人Gaucher病Ⅰ型は進行性で重症であることが報告されている[1]．また，病型別分布に関しては，Gaucher Registry（おもな患者登録国は米国，イスラエル，ブラジル．日本人患者全体のデータは含まれていない）の2009年Annual Report[2]によると，登録患者でデータのある5,140名のうち，Ⅰ型は4,720名（92%），Ⅱ型56名（1%），Ⅲ型364名（7%）と報告されているのに対し，厚生労働省難治性疾患克服事業の「ライソゾーム病（ファブリー病を含む）に関する調査研究班」の報告書（主任研究者　衛藤義勝，http://www.japan-lsd-mhlw.jp/lsd_doctors/gaucher.html）によると，日本人Gaucher病では，Ⅰ型37.4%，Ⅱ型27.9%，Ⅲ型34.7%と報告されている．また経過中，Ⅰ型からⅢ型へ病型が変化する症例が存在することが報告されている[3]．

以上のように，欧米人に比べ日本人Gaucher病患者では，Ⅰ型においては重症であり，また神経型患者の発生頻度が高いことが明らかにされている．

2．治　療

Gaucher病に対する治療は，現在，酵素補充療法が一般的に普及している．セレザイム®〔イミグルセラーゼ（遺伝子組換え），ジェンザイム社，以下イミグルセラーゼとする〕は，酵素補充療法製剤であり，1998年にわが国で承認・発売開始になっている．現在60か国以上で承認されており，6,000例以上のGaucher病患者が本剤による治療を受けている．海外におけるGaucher病Ⅰ型患者に対するイミグルセラーゼによる10年間の治療効果については，ヘモグロビン値，血小板数，脾臓および肝臓容積は改善し，その効果は持続することが報告されている[4]．また，1994～2004年の10年間に世界的に行われた市販後調査および免疫学的な調査を通じて収集されたデータの解析をもとに，多数例においてその安全性が報告されている[5]．しかしながら，日本人Gaucher病患者に対するイミグルセラーゼの長期間にわたる有効性および安全性についてのまとまった報告はない．

そこで今回われわれは，欧米人と臨床表現型の異なる日本人Gaucher病患者に対するイミグルセラーゼによる酵素補充療法の8年間の有効性および安全性について検討したので報告する．

対象と方法

1．対　象

1998年3月～2006年3月までの8年間にイミグルセラーゼの市販後調査に登録された155例（87施設）のうち，調査票回収不能3例，転院などによる重複症例42例を除く110例を調査対象症例とした．このうち，適応外使用1例，以前の酵素補充療法治療歴がある（アルグルセラーゼの投与歴，イミグルセラーゼの治験症例など）55例，投与開始時の有効性評価項目がすべて未記載の3例の計59例を除いた51例を有効性の解析対象とした．安全性については調査対象症例全例（110例）を対象とした．病型の診断は担当医師により行われた．

2．方　法

1）有効性

有効性については，ヘモグロビン値，血小板数，アンジオテンシン変換酵素（angiotensin converting enzyme，以下ACEと略す）値，酸性ホスファターゼ（acid phosphatase，以下ACPと略す）値，および肝・脾臓容積（MRIまたはCTによって測定）の変化について検討を行った．ヘモグロビン値については，貧血の定義[6]を12歳以上の男性12.0 g/dL以下，同女性11.0 g/dL以下，2歳以上12歳未満10.5 g/dL以下，6か月以上2歳未満9.5 g/dL以下，6か月以下乳児10.1 g/dL以下とし，貧血の有無を判定した．血小板減少の重症度[7]については，軽度を10万/mm³以上12万/mm³未満，中等度6万/mm³以上10万/mm³未満，重度を6

万/mm³未満とした.

2) 安全性

安全性については，副作用および抗イミグルセラーゼIgG抗体（以下，IgG抗体と略す）産生率と過敏症発現について検討した．イミグルセラーゼによる治療開始後に発現したすべての好ましくない事象（疾患，症状，臨床検査値異常）を有害事象とし，そのうち担当医師の判断により本剤との因果関係が否定できないものを副作用とした．また，IgG抗体は担当医師が必要と判断した場合に測定を行い，測定はジェンザイム社で実施された.

結果

1. 患者背景（表1）

有効性の解析対象とした51例の患者背景は，男性31例（60.8%），女性20例（39.2%），病型はⅠ型が18例（35.3%），Ⅱ型16例（31.4%），Ⅲ型17例（33.3%）であった．治療開始時（ベースライン）の年齢は，Ⅰ型およびⅢ型は幅広い分布を示していたが，Ⅱ型はすべて1歳以下であった．ベースラインにおいて，貧血は17例（33.3%）に認められた．血小板減少は30例（58.8%）に認められ，その重症度の内訳は軽度2例（3.9%），中等度16例（31.4%），重度12例（23.5%），であった．脾臓の一部または全摘出歴のある症例は10例（19.6%）であった．イミグルセラーゼの投与期間中央値は197週（最大420週，最小52週）であり，平均投与間隔は14.0±3.2日，平均1回投与量はⅠ型56.4±7.0単位/kg，Ⅱ型85.9±24.1単位/kg，Ⅲ型67.0±16.3単位/kgであった.

2. 有効性

有効性については，ヘモグロビン値，血小板数，肝・脾臓容積，ACE値，ACP値を指標として検討を行った.

1) ヘモグロビン値（図1）

51例のうち，ヘモグロビン値が測定されていない2例および脾臓摘出歴のある10例を除く39症例におけるヘモグロビン値は，ベースラインの平均10.1±2.4 g/dLから，24週目には平均12.2±1.5 g/dLへと改善し，以後，平均値は投与408週目まで12.0 g/dL以上を維持していた.

2) 血小板数（図2）

51例のうち，血小板数が測定されていない2例および脾臓摘出歴のある10例を除く39症例での血小板数は，ベースラインの平均10.3±7.0×10^4/mm³から，治療16週目には平均16.1±8.3×10^4/mm³と正常値まで改善した．以後，徐々に増加傾向を示し，治療408週目では平均22.8±16.6×10^4/mm³であった.

3) 肝・脾臓容積の減少率（図3）

肝臓容積については，減少率を検討できた症例数は15例であり，平均肝臓容積減少率は，治療開始後24週8%（n＝6），48週20%（n＝10），72週14%（n＝10），96週31%（n＝6）であった．脾臓容積については，減少率が検討できた症例数は16例であり，平均脾臓容積減少率は，治療開始後24週45%（n＝6），48週48%（n＝11），72週43%（n＝10），96週では59%（n＝6）であった.

4) アンジオテンシン変換酵素値（ACE）（図4）

「日本人小児の臨床検査基準値」[6]をもとに，18歳以上を成人（基準値：8.3～21.4 U/L），18歳未満を小児（基準値：6.7～35.6 U/L）として検討した．その結果，成人では，ベースラインで平均47.1±29.9 U/L（n＝14）であったが，治療開始とともに低下し，治療開始24週後には平均19.8±7.5 U/L（n＝6）と正常化した．以降，ほぼ正常範囲内で推移し，408週後では平均14.8±4.5 U/L（n＝3）であった.

一方，小児ではベースラインで平均91.6±34.3 U/L（n＝32）と成人に比較して高値であったが，治療開始とともに低下し，24週後には平均32.7±10.7 U/L（n＝17）と正常化した．以降も正常範囲内で推移し，384週後では平均35.6±21.9 U/L（n＝3）であった.

表1　有効性評価対象の患者背景

項　目	分　類	症例数	
性　別	男	31	60.8%
	女	20	39.2%
病　型	Ⅰ型	18	35.3%
	Ⅱ型	16	31.4%
	Ⅲ型	17	33.3%
治療開始時年齢（歳）	Ⅰ型	28.1±22.5	中央値：26 最小：0.3 最大：66
	Ⅱ型	0.8±0.2	中央値：0.9 最小：0.3 最大：1
	Ⅲ型	11.7±17.2	中央値：2 最小：0.7 最大：51
貧血の有無	なし	32	62.7%
	あり	17	33.3%
	不　明	2	3.9%
血小板減少症	なし	17	33.3%
	あり　軽　度	2	3.9%
	あり　中等度	16	31.4%
	あり　重　度	12	23.5%
	不　明	2	3.9%
脾臓摘出歴	なし	41	80.4%
	あり（全摘）	9	17.6%
	あり（部分切除）	1	2.0%
投与期間（週）		281±123	中央値：197 最小：52 最大：420
投与間隔（日）		14.0±3.2	中央値：13.3 最小：6.3 最大：26.2
1回投与量（単位/kg）	全症例	68.9±20.5	中央値：59 最小：45 最大：136
	Ⅰ型	56.4±7.0	中央値：56 最小：45 最大：72
	Ⅱ型	85.9±24.1	中央値：81 最小：59 最大：136
	Ⅲ型	67.0±16.3	中央値：57 最小：53 最大：96