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Case report

Hypoparathyroidism and facial dysmorphism as main symptoms of 22q.11 deletion syndrome

Hideto Yoshikawa*, Tokinari Abe

Department of Pediatrics, Niigata City General Hospital, 2-6-1 Shichikuyama, Niigata 950-8739, Japan

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Abstract

A 12-year-old Japanese boy with mental retardation and facial dysmorphism developed frequent convulsions, and hypocalcemia due to hypoparathyroidism was recognized. Chromosomal analysis involving the fluorescence in situ hybridization method revealed a microdeletion of 22q11.2. However, other laboratory examinations revealed no cardiac anomaly, thymic hypoplasia, or cleft palate. It is well known that typical cases of 22q11 deletion syndrome have a cardiac anomaly, thymic hypoplasia and a cleft palate. However, the phenotype of 22q11 deletion syndrome is diverse, and hypoparathyroidism and facial dysmorphism have been reported in nine cases, including this case, associated with 22q11 deletion. This combination of clinical manifestations could be given another term, such as hypoparathyroidism-facial syndrome. Some hypoparathyroidism patients due to 22q11.2 deletion may be misdiagnosed as having idiopathic hypoparathyroidism, and a child diagnosed as having hypoparathyroidism should be examined for chromosomal 22q.11.2. deletion.
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Keywords: Hypoparathyroidism; 22q.11 Deletion syndrome; Dysmorphism; 'CATCH 22'

1. Introduction

The major phenotypes of chromosome 22q11 deletion syndrome are velo-cardio-facial syndrome, DiGeorge syndrome, and conotruncal anomaly face syndrome. The anonym 'CATCH 22' (Cardiac anomaly, Abnormal faces, Thymic hypoplasia, Cleft palate and Hypocalcemia) has been proposed to describe these phenotypes. On the contrary, this anonym is also thought to be inappropriate, because there are many atypical cases and an abnormal face is not a proper term. Thus, 22q.11 deletion syndrome has been considered a more descriptive term because it includes every phenotype of 22q11 deletion.

Although 22q11 interstitial deletion is one of the most frequent causes of chromosomal aberration syndromes, there is wide variability in the clinical spectrum. Thus, 22q11 deletion syndrome is likely to be underdiagnosed, especially in mildly affected individuals, and the awareness of such cases is necessary for accurate diagnosis of 22q11 deletion.

Cases of 22q11 deletion syndrome with accompanying isolated hypoparathyroidism and facial dysmorphism have been rarely reported [1–3]. We report here another one, and review the previously reported cases.

2. Case report

This 12-year-old Japanese boy was born without asphyxia. At seven days of age, he developed generalized convulsions several times. Thus he was referred to our neonatal intensive care unit. Routine laboratory examination disclosed no abnormal findings except for hypocalcemia (Ca 5.8 mg/dl). Brain computed tomography revealed no abnormal findings. The hypocalcemia was treated by intravenous administration of calcium, resulting in normalization of the serum calcium level. His neonatal hypocalcemia was considered to be transient, and parathyroid hormone was not examined at that time. Thereafter, he did not visit our hospital until 12 years of age because he had had no seizures. However, his parents noticed his developmental delay.

At 12 years of age, he developed generalized tonic-clonic convulsions lasting for 1–2 min during sleep, the frequency of which gradually increased. Two months after the initiation of his convulsions, a generalized convulsion continued for more than 30 min and so he was transferred to our hospital. When he arrived at our hospital, his seizures had

* Corresponding author. Tel.: +81-25-241-5151; Fax: +81-25-248-3507.
E-mail address: hideto@hosp.niigata.niigata.jp (H. Yoshikawa).

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Table 1
Summary of laboratory data[a]

Ca	6.1 mg/dl	Free T3	3.33 pg/ml
Ionized Ca	0.82 mmol/l (0.93–1.21)	Free T4	0.89 ng/dl
IP	8.9 mg/dl	TSH	2.730 μIU/ml
ALP	908 IU	LH	1.56 mIU/ml
CK	406 IU	FSH	2.52 mIU/ml
PTH-C terminal	< 0.6 ng/ml (<1.3)	Lactate	15.9 mg/dl
PTH-intact	< 2.0 pg/ml (10–65)	Pyruvate	0.9 mg/dl
Calcitonin	24.1 pg/ml	BS	123 mg/dl
1a,25-$(OH)_2$ Vit D3	35.4 pg/ml (20.0–60.0)	CD4/8	0.71
T cell	83%	B cell	6%

[a] Ca, calcium; IP, inorganic phosphate; ALP, alkaline phosphatase; CK, creatinine kinase; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; LH, lutenizing hormone; FSH, follicle-stimulating hormone; BS, blood sugar.

already ceased and his consciousness was alert. His body height was 151 cm (±0.25 SD), body weight 52 kg (±1.1 SD), and head circumference 53.5 cm (±0.3 SD). Physical examination revealed no abnormal findings except for obesity and a mild dysmorphic facial appearance, such as an upslanting narrow palpebral fissure, hypertelorism, a nose with a broad nasal root and small nasal alae, a mildly hypoplastic mandible, and a small mouth. He had no overt or submucous cleft of the palate. However, he was suspected to have nasopharyngeal insufficiency due to his nasal speech. Neurological examination disclosed no abnormal findings. Routine laboratory examinations revealed hypocalcemia, hyperphosphatasia and a marked decrease in parathyroid hormone (Table 1). The Ellsworth–Howard test was performed, and renal tubular responsiveness to exogenous parathyroid hormone infusion was confirmed. Brain computed tomography (CT)revealed multiple calcification in the dentate nucleus, thalamus, putamen, globus pallidus, caudate and subcortical white matter (Fig. 1). Magnetic resonance imaging (MRI) revealed no abnormal findings in the lesions in which calcification was observed on CT. Cardiac and abdominal ultrasonography revealed no abnormal findings. Electroencephalography revealed equivocal spikes in the bilateral occipital areas. Fundoscopic examination revealed bilateral papillo-edema of the optic nerve. His intelligence quotient was estimated to be 54. As regards chromosome analysis, G-banding showed no chromosomal aberration, and a fluorescence in situ hybridization (FISH) study involving a specific probe of the 22q11.2 region (TUPLE-locus) revealed a fluorescence signal in only a single chromosome, which is consistent with del 22q11.2.

After admission, he was treated by supplementation of calcium and alfacalcitrol, and the oral administration of valproic acid was also started. Two days after admission, the seizures had ceased completely. The serum calcium level increased, eventually becoming normalized.

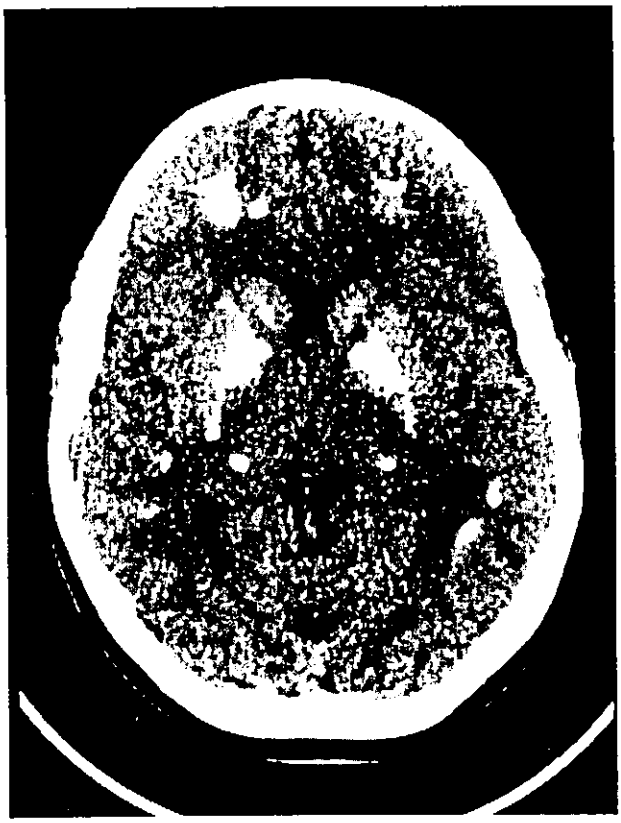

Fig. 1. Brain CT findings. Brain CT showed multiple calcification in the dentate nucleus, thalamus, putamen, globus pallidus, caudate and subcortical white matter.

3. Discussion

Although clinical features such as a cardiac anomaly, thymic hypoplasia and a cleft palate are the major symptoms of 22q11 deletion syndrome, cases of 22q11 deletion syndrome with hypoparathyroidism and mild dysmorphism, not accompanied by a cardiac anomaly, thymic hypoplasia or a cleft palate, have rarely been reported. To the best of our knowledge, there have been eight reported cases with hypoparathyroidism and a dysmorphic face as main symptoms [1–3] (Table 2). Adachi et al. [1] reported ten patients diagnosed as having hypoparathyroidism associated with 22q11 deletion, five of whom did not also have a cardiac anomaly, thymic hypoplasia, or a cleft palate. This combination of clinical manifestations might be part of the spectrum of 22q.11.2 deletion syndrome.

Cohen et al. [4] and Lipson et al. [5] reported cases with hypoparathyroidism, mental retardation and dysmorphic features, who are very similar to our case; however, a FISH study was not performed in their cases. Sanjad et al. [6], Kalam et al. [7], and Richardson et al. [8] also reported cases with hypoparathyroidism, dysmorphic features and severe growth failure. These cases were also similar to our case, except for the growth failure. In these cases, a FISH study was also not performed. Although we could not determine whether these cases were due to a 22q11 deletion, we could not rule out that these reported similar cases might be part of the spectrum of 22q.11 deletion syndrome.

Table 2
Reported cases of 22q.11 deletion syndrome with hypoparathyroidism and facial dysmorphism as main symptoms[a]

Case	Age at Dx	Age/sex	Cardiac anomaly	Thymic hypoplasia	Cleft palate/NPI	Dysmorphic face	Mental retardation (IQ)	HP	ICC	Conv	Ref.
1	9 d	13 y/M	−	−	−/−	+	+ (71)	+	+	+	[1]
2	4 m	21 y/F	−	+?	−/−	+	+ (46)	+	+	+	[1]
3	7 m	8 y/M	−	−	−/+	+	+ (77)	+	−	+	[1]
4	1 y	14 y/F	−	−	−/−	+	+ (57)	+	−	+	[1]
5	1 y	13 y/F	−	−	−/+	+	+ (51)	+	N.T.	+	[1]
6	17 y	18 y/M	−	−	−/+	+	+ (54)	+	+	+	[2]
7	15 y	16 y/M	−	−	−/+	+	+ (76)	+	+	+	[2]
8	18 m	18 m/M	−	−	−/−	+	? (83)	+	N.T.	+	[3]
Present case		12 y/M	−	−	−/+	+	+ (54)	+	+	+	

[a] Case 2 was suspected to have thymic hypoplasia because of frequent infections [1]. However, this is uncertain and thus this case is included in this table. d, days; m, months; y, years; Dx, diagnosis; NPI, nasopharyngeal insufficiency; IQ, intelligence quotient; HP, hypoparathyroidism; ICC, intracranial calcification; N.T., not tested; Conv, convulsion.

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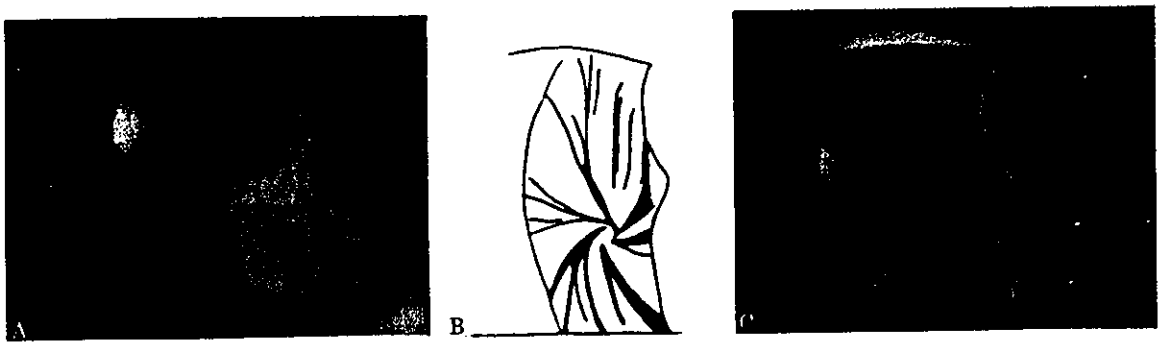

Figure. Slit-lamp examination of cornea revealed white-colored, whorl-like corneal opacity with a radial pattern. (A) Normal cornea, (B) cartoon drawing of C, and (C) the patient's current figure.

Clinical diagnosis of Fabry disease Whorl-like corneal opacity

Hideto Yoshikawa, MD and Izumi Ogawa, MD, Niigata, Japan

An 11-year-old Japanese girl preserved with eye itching and mild hypesthesia in her extremities. Her hidrosis was decreased, and her body temperature was approximately 37 °C. Family history was not contributory. Routine laboratory and physical examinations revealed no abnormal findings. Cardiac and renal function was normal. Ophthalmologic examination with a slit-lamp disclosed bilateral whorl-like corneal opacity (figure). The α-galactosidase activity in leukocytes was markedly decreased, and a point mutation of the *α-galactosidase A* gene was detected. Thus, she was diagnosed as a female carrier of Fabry disease. Whorl-like corneal opacity is a characteristic ocular manifestation of Fabry disease, even if the patient is asymptomatic or heterozygous.[1,2]

Address correspondence and reprint requests to Dr. Hideto Yoshikawa, Department of Pediatrics, Niigata City General Hospital, 2-6-1 Shichikuyama, Niigata 950-8739, Japan; e-mail: hideto@hosp.niigata.niigata.jp

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Letter to the Editors

Sudden respiratory arrest and Arnold-Chiari malformation

When a seven-year-old healthy Japanese boy had a shower after swimming in the sea, he vomited and became drowsy. He was transferred to hospital, and on admission, was drowsy and his respiration irregular. During examination, his respiration stopped suddenly, and he was put on mechanical ventilation. Pyrexia and dehydration were not present. His blood pressure and cardiac rhythm were stable. Physical examination disclosed no abnormal findings except the respiratory insufficiency and unconsciousness. Routine laboratory examination revealed no abnormal findings. Brain CT was normal. He remained on mechanical ventilation for 2 hours, and 4 hours later, spontaneous respiration became stable. Next morning, his consciousness became clear and that afternoon he could speak and eat food. EEG showed no abnormalities. MRI revealed no abnormal findings except for cerebellar tonsil downward shift, which was consistent with Chiari malformation type 1 (Fig. 1). Although the etiology of this episode is unclear, the most probable explanation might be a sudden compression of brain stem due to Chiari malformation. In Chiari malformation, sleep apnoea and Ondine's curse have been reported.[1,2] However, sudden respiratory arrest during awake state has not been described. We wish to draw attention to sudden respiratory arrest during awake state, which may lead to death if no medical support is provided, in patients with Chiari malformation.

Figure 1 MRI findings of brain (sagittal T2 weighted images) demonstrated downward sift of the cerebellar tonsils through the foramen magnum.

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Hideto Yoshikawa*
Department of Pediatrics,
Niigata City General Hospital,
Niigata, Japan
E-mail address: hideto@hosp.niigata.niigata.jp

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*Correspondence: Hideto Yoshikawa, MD, Department of Pediatrics, Niigata City General Hospital, 2-6-1 Shichikuyama, Niigata 950-8739, Japan. Tel.: +81-25-241-5151; fax: +81-25-248-3507.

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Benign "Setting Sun" Phenomenon in Full-Term Infants

ABSTRACT

I report two normally developed infants showing benign" setting sun" phenomenon. A 2½-year-old boy and a 7-year-old boy, who were born without any complications at full term, developed brief episodes of downward gazing during sucking and crying after birth. However, there were no other clinical or laboratory findings, and they developed normally. The phenomenon was not visible until 6 months and 7 months, respectively. The "setting sun" phenomenon usually indicates underlying severe brain damage and can also be seen, although rarely, in healthy full-term infants until 1 to 5 months. However, the benign "setting sun" phenomenon might exist until 6 or 7 months of age in normal infants. (*J Child Neurol* 2003;18:424–425).

The "setting sun" phenomenon is a well-known sign associated with severe neurologic disorders such as hydrocephalus and kernicterus.[1,2] It has also been reported that the phenomenon can also be seen, although rarely, in healthy full-term infants until 1 to 5 months[3–7]; however, downward gazing in full-term normal infants has not been fully investigated. I report here two normally developed infants who showed the transient "setting sun" phenomenon until 6 and 7 months of age, respectively.

Case Report

Case 1

A 2½-year-old Japanese boy was born at 40 weeks of gestation, weighing 3410 g, without any complications. The family history was not contributory. Two days after birth, although he was well, he developed a spontaneous downward gazing for several seconds. His downward gaze became frequent, especially before and after feeding of breast milk or during crying, until the fourth day after birth, when he was transferred to our hospital. On admission, physical and ophthalmologic examinations revealed no abnormal findings. Routine laboratory examinations also revealed no abnormal findings. Brain computed tomography (CT) also revealed no abnormal findings. An interictal electroencephalogram (EEG) and an EEG when his downward gazing was observed were both normal. The most effective way to provoke the phenomenon was flexion of the neck in the supine position, as in rising from a lying to an upright position. The downward gazing was not repetitive or persistent. Optokinetic nystagmus was also observed. At 4 months of age, he could control his head and smile well, but the downward gazing remained, however, and still occurred once a week. Thereafter, the frequency of the phenomenon decreased gradually and disappeared at 6 months of age. At 7 months of age, he could sit alone. At 1 year of age, he could walk alone. He could utter some jargon, and his recognition of words was good enough for his age. He developed normally and experienced neither seizures nor neurologic symptoms until the age of 2½ years.

Case 2

A 7-year-old boy was born by caesarean section at 40 weeks of gestation, weighing 2588 g. Asphyxia was not noted. After birth, his mother noticed that his eyes dropped during sucking of milk and bathing, which was precipitated by stimulation. The phenomenon could consist of downward deviation of the eyes, with upper eyelid retraction, a rim of sclera being visible above each iris. Mild jaundice was noted with a maximum billirubin level of 10.3 mg/dL, which was treated with phototherapy on days 3 and 4. Physical examination revealed no abnormal findings. Eye movement was normal. At 1 month of age, the eye dropping had decreased to once or twice a week. Visual fixation was seen. Cranial ultrasonography, brain CT, and EEG revealed no abnormal findings. At the age of 3 months, the "setting sun" sign was no longer seen. He achieved head control at 4 months, rolling over at 6 months, and sitting alone at 7 months of age. However, at 6 months of age, the downward gazing developed again, two to three times per day, during alteration of position but disappeared by 7 months of age. Thereafter, he developed normally without any neurologic signs until the age of 7 years.

Discussion

Two patients developed frequent brief episodes of conjugate downward gazing, which occurred until 6 and 7 months, respectively. Their brief downward gazing was elicited most prominently by stimulation, especially alteration of the position in the vertical plane. The reason the phenomenon disappeared transiently from 4 months to 6 months is unknown in case 2. However, the phenomenon was considered to be benign, which did not suggest latent brain impairment.

The "setting sun" phenomenon usually indicates severe brain damage and has been reported in preterm babies and children with severe developmental disabilities. Willi reported that the "setting sun" phenomenon beyond 12 weeks of age suggests the existence of permanent brain damage, such as kernicterus.[1] Yokochi et al described 13 infants examined at 2 to 8 months corrected age with histories of preterm birth or perinatal asphyxia and developmental delay who exhibited multiple episodes of downward gazing lasting several seconds each during wakefulness.[2] When examined later, all were found to be mentally retarded with cerebral palsy. Kleiman et al reported five preterm infants who had episodes of conjugate downward gazing 2 to 3 months after birth.[8] The authors concluded that transient conjugate downward gazing in neurologically healthy preterm infants can often be a benign phenomenon owing to immature myelination of vertical eye movement systems and immaturity or dysfunction of extrageniculocalcarine visual pathways.

Transient paroxysmal downward gazing appears to occur as a benign phenomenon in neurologically healthy full-term infants. Hoyt et al reported that prolonged tonic downward deviation of the eyes during wakefulness developed in 5 of 242 healthy term infants, which resolved by 6 months of age with no neurologic sequelae.[3] Miller and Packard reported 12 term infants noted to exhibit paroxysmal downward gazing in the neonatal period.[4] They developed normally, and the phenomenon was prolonged until 1 to 5 months of age. Haverkamp and Weimann reported familial cases of benign "setting sun" phenomenon among healthy newborns, which lasted until 10 weeks of life.[5] Lenora and Morales reported three healthy term neonates exhibiting paroxysmal downward gazing, beginning on the first day of life, and one of them showed the phenomenon until 4 months.[6] Cernerud reported that the "setting sun" phenomenon can be elicited by alteration of the position in normal infants younger than 4 weeks of age and that there is a marked response to removal of light in normal infants between 8 and 20 weeks of age.[7] The phenomenon elicited by removal of light might be the same as the eye popping reflex of healthy infants reported by Perez.[9]

Ocular bobbing is a descriptive term for abnormal vertical eye movements that are usually seen during coma, anoxia, status epilepticus, and metabolic encephalopathy, and it implies a poor prognosis.[10] So ocular bobbing never develops in normal infants like our patients. Epileptic attacks might be another possible cause. The downward gazing is so episodic that it can be confused with epileptic seizures. We could not rule out epilepsy in case 2 because an ictal EEG was not performed. However, his clinical episodes seemed to be a reflex, and even if they represented epilepsy, it could have been benign because the episodes ceased spontaneously.

The "setting sun" phenomenon associated with hydrocephalus probably results from pressure-induced dysfunction of the vertical gaze centers in the tectum. However, this is not a probable mechanism in normal healthy infants. During infancy, motor activity largely comprises a reflex and postural reaction. Although the mechanism underlying the downward gazing in normal neonates and infants is unknown, the "setting sun" phenomenon might be related to the presence of a normal oculocephalic response. I considered that it might represent a maturation delay in one of the reflex systems involved in eye movements, and benign "setting sun" phenomenon probably occurs more frequently than has been reported. In conclusion, this report suggested that the phenomenon occurs by 6 or 7 months of age even in normally developed infants.

Hideto Yoshikawa, MD
Department of Pediatrics
Niigata City General Hospital
Niigata, Japan

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Address correspondence to Dr Hideto Yoshikawa, Department of Pediatrics, Niigata City General Hospital, 2-6-1 Shichikuyama, Niigata 950-8739, Japan. Tel: 81-25-241-5151; fax: 81-25-248-3507; e-mail: hideto@hosp.niigata.niigata.jp.

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Mounting evidence implicates genetic factor(s) in the pathogenesis of CH. Two studies of small CH pedigrees did not identify a clear mechanism of transmission.[3] An autosomal dominant inheritance was postulated in several CH families on the basis of a large epidemiologic study.[4] Mitochondrial DNA mutations have been described in a single CH case.[5] The current study excludes such models of inheritance in our kindred, suggesting that also the autosomal recessive pattern could occur in CH.

Genes encoding ionic channels, as demonstrated for familial hemiplegic migraine, receptors and carriers for neural amines, G-proteins, and others[6] are CH-causing candidates. An involvement of different genes could give rise to different models of inheritance, and the variable penetrance of mutations in different genes could cause underestimation of familial CH.

The affected individuals of our kindred apparently display a typical clinical illness, with the only notable difference in the unusually high prevalence of affected females (female/male ratio 3:1), which contrasts with previous studies.[7] A putative familial form of CH is less likely to be affected by the sexual factor than the sporadic form, but such a hypothesis is not supported by statistical evidence because of the small number of cases identified. On the other hand, such phenotypic variables as temporal pattern (i.e., chronic or episodic) and side expression were discordant within the eight affected members of our kindred (see table E-1 on the *Neurology* Web site). Discordance of CH side expression has been described in monozygotic twins.[2] These variables could be influenced by environmental agents or by modifier genes inherited independently from the disease gene(s), as found in other genetic disorders.

In conclusion, analysis of large families and the personal examination of each member suspected of having CH are useful to identify particular families and to reveal the pattern(s) of inheritance of CH. Our data suggest that an autosomal recessive mechanism of inheritance adds to the known models postulated for CH.

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Address correspondence and reprint requests to Dr. R. De Simone, Clinical Neurologica, Università di Napoli "Federico II," via S. Pansini 5, I-80131 Naples, Italy; e-mail: rodesimo@unina.it

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EDTA-dependent pseudothrombocytopenia induced by valproic acid

Hideto Yoshikawa, MD

Pseudothrombocytopenia is a falsely low platelet count due to platelet clumping that occurs in anticoagulated blood at room temperature.[1,2] Automatic analyzers therefore yield falsely low counts because they cannot count platelet clumps correctly. Pseudothrombocytopenia results when antiplatelet autoantibodies bind to platelet surface glycoproteins that are modified or exposed by the combined action of anticoagulant and low temperature.[2] This occurs most often in blood samples anticoagulated with ethylenediaminetetra-acetic acid (EDTA), although citrate, oxalate, and heparin have also been implicated. Its frequency was estimated to be 0.09 to 0.13%. However, other factors, including drugs, may also be involved.

Case report. A 1-year 9-month-old Japanese girl was born without any complications. Family history was unremarkable. She developed normally until 1 year 2 months of age when afebrile seizures developed with an initial frequency of three times a day. EEG disclosed no abnormal findings. At 1 year 6 months, she experienced afebrile seizures lasting for 1 to 2 minutes several times a day, and the administration of phenobarbital was begun without effect. On admission to our hospital, she was afebrile. Physical examination was normal. Routine laboratory examinations were normal, with the blood cell counts as follows: leukocytes 5.8 × $10^3/\mu L$, hemoglobin 11.9 g/dL, and platelet count 245 × $10^3/\mu L$ without any aggregation in EDTA-anticoagulated blood. A repeated complete blood count showed similar results. Brain CT and interictal EEG revealed no abnormal findings, and the etiology of the seizures was not proven. Phenobarbital was replaced by valproic acid at 200 mg/day, and seizures stopped. Five days after the initiation of valproic acid, the platelet count was 5.0 × $10^3/\mu L$, with platelet aggregation in EDTA-anticoagulated blood (figure). However, there was no bruising or hemorrhage. The serum concentration of valproic acid was 50 μg/mL. A repeat platelet count was 7.0 × $10^3/\mu L$ in EDTA-anticoagulated blood, but the platelet count was 234 × $10^3/\mu L$ without any aggregation in heparin-anticoagulated blood. Platelet autoantibodies were negative with mixed passive hemoagglutination test. There were no other hematologic abnormalities, including prothrombin time, fibrinogen level, and fibrin degenerated product level. Valproic acid was replaced by phenobarbital, and 1 week later, the decreased platelet count had normalized in both EDTA- and heparin-anticoagulated blood.

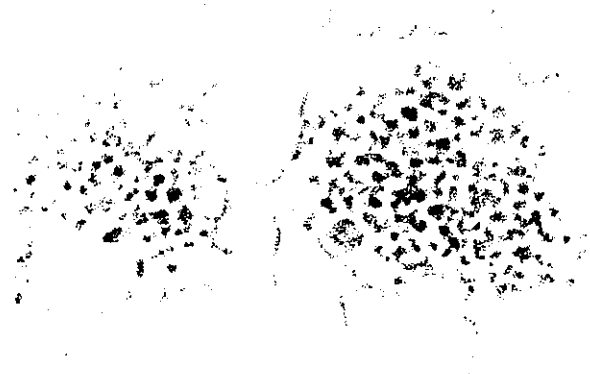

Figure. Platelet clumps in ethylenediaminetetra-acetic acid–anticoagulated blood. May/Grünwald/Giemsa–stained blood film on light microscopy; ×400.

Discussion. Her clinical course and laboratory data were compatible with valproic acid–induced EDTA-dependent pseudothrombocytopenia. Valproic acid can cause hematopoietic toxicity, most frequently involving platelets, with either thrombocytopenia or platelet dysfunction. Bone marrow suppression affecting all three cell lines has been also reported. Autoantibodies to platelets and a direct effect on platelets were suspected to be the mechanism underlying thrombocytopenia due to valproic acid.[3-5] An autoimmune thrombocytolysis has been suggested based on the similar molecular configuration of valproic acid to that of platelet

cell membrane fatty acids and the finding of antiplatelet antibodies. Although the pathophysiology of the valproic acid–induced EDTA-dependent pseudothrombocytopenia remains unclear and might be different from valproic acid–induced thrombocytopenia, the structure of valproic acid might have some relationship to the etiology.

Although pseudothrombocytopenia induced by mexiletine has been reported,[6] as has pseudothrombocytopenia induced by valproic acid,[7] there is no other evidence that the presence of pseudothrombocytopenia is associated with the use of specific drugs. In the previously reported similar case,[7] the patient was a 25-year-old man with epilepsy, treated with valproic acid monotherapy. Platelet count was $3.6 \times 10^4/\mu L$ in EDTA-anticoagulated blood and $28.5 \times 10^4/\mu L$ in heparin-anticoagulated blood. Because thrombocytopenia is not uncommon when valproic acid is administered, the possibility of EDTA-dependent pseudothrombocytopenia ought to be considered, especially in the absence of unusual bruising or bleeding.

From the Department of Pediatrics, Niigata City General Hospital, Japan.

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Address correspondence and reprint requests to Dr. H. Yoshikawa, Department of Pediatrics, Niigata City General Hospital, 2-6-1 Shichikuyama, Niigata 950-8739, Japan; e-mail: hideto@hosp.niigata.niigata.jp

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Infancy onset hereditary spastic paraplegia associated with a novel atlastin mutation

F. Dalpozzo, MD; M.G. Rossetto, MS; F. Boaretto, MS; E. Sartori, MS; M.L. Mostacciuolo, PhD; A. Daga, PhD; M.T. Bassi, PhD; and A. Martinuzzi, MD, PhD

Cerebral palsy is the most common cause of spastic paraplegia affecting infants. However, spasticity characterized by progressive gait impairment may also be the first sign of infantile onset hereditary spastic paraplegia (HSP).[1]

We studied a family with six affected members (figure).

The first patient (II-3) had slowly progressive leg spasticity and weakness that started in infancy. She and her second son (III-2) had mild cyanosis at birth, and for that reason their first diagnosis was cerebral palsy.

The clinical history is similar for all affected members: normal pregnancy and delivery, motor impairment starting before gait acquisition, and normal cognitive and language development.

Clinical characteristics are summarized in table E-1 (see www.neurology.org). All affected members presented delayed motor milestones and gait impairment. There was no sphincteric disturbance.

Current neurologic examination revealed severe spastic paraparesis, distal atrophy, and weakness in lower limbs. In Cases II-3 and III-2, we also found distal mild atrophy in upper limbs and a slight impairment in fine hand movements (table E-1; see www.neurology.org). They underwent brain and spinal MRI, which had normal results. Subjects II-1 and II-2 did not report any motor impairment and were not examined.

All affected members were investigated neurophysiologically (visual, somatosensory, and motor evoked potentials, nerve conduction velocities, EMG). The main features were prolonged central motor conduction time and absent or very small somatosensory potentials evoked from lower limbs. In Patients II-3 and III-2 we also found chronic neurogenic EMG changes in upper limbs. Auditory, ophthalmologic, and neuropsychological examinations all had normal results. Genomic DNA was purified from peripheral blood leukocytes. Linkage analysis (MLINK program of the LINKAGE package) was performed using the most informative markers linked to *SPG3*, *SPG4*, *SPG8*, *SPG9*, *SPG10*, and *SPG12*. Sequence analysis was performed on amplimers obtained with appropriate primers using an automatic sequencer.[2]

Significant negative lod scores (<-2 at recombination fraction $\theta = 0$) were obtained for all loci but *SPG3*. Sequencing of the entire *SPG3A* gene showed a heterozygous mutation in exon 12. This A to G transition at position 1222 changes the conserved methionine in position 408 into valine. This mutation was present in all affected family members but not in the two nonaffected siblings or the first child of the index case (II-3), or in 100 control chromosomes. The unaffected brother (II-1) of the index case (II-3) inherited a haplotype that segregated with the disease but had normal amino acid sequence of the *SPG3A* gene (see the figure).

SPG3A was found associated with mutations in the gene encoding the novel protein atlastin. Four different *SPG3A* mutations were reported.[2,3] All four missense mutations fall within exons 7 and 8 of the *SPG3A* gene.[2,3] A novel frameshift mutation in exon 12 leading to premature protein termination was recently described,[4] but in this pedigree the disease was milder and some cases developed the first clinical signs in their adulthood.

The clinical presentation of HSP in the family described here is the earliest reported onset for autosomal dominant HSP.[1] Because of the very early onset, the first patients were misdiagnosed during infancy with cerebral palsy, and the index case was unaware she had a genetically transmissible disease. A peculiar sign is the hand mild atrophy and the EMG chronic neurogenic pattern, implying a possible involvement of spinal motoneurons in the degenerative process. In the last generation, only the oldest affected son of the index case exhibited this sign, suggesting that it may be related to disease duration. Taking into consideration the young age of the other members we cannot establish if the involvement

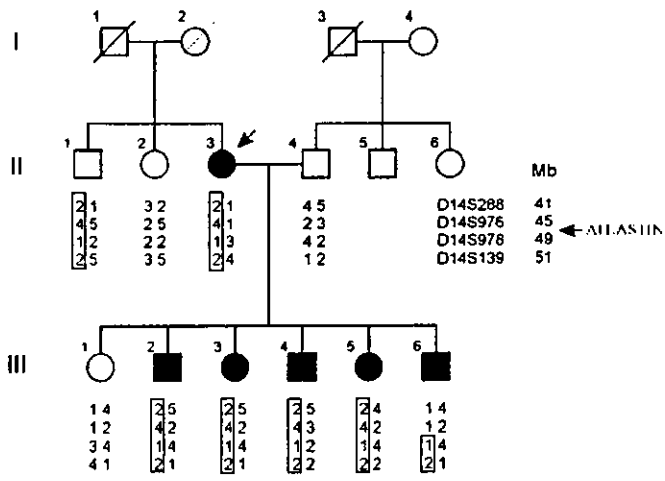

Figure. Pedigree of the family with SPG3A. *Arrow indicates the index case; blackened and unblackened symbols represent affected and unaffected individuals. Physic map is according to information from the UCSC Genome Browser. Boxes represent the disease-bearing chromosome.*

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 26 issue to find the title link for this article.

ELSEVIER

Transient Parkinsonism in Bilateral Striopallidodentate Calcinosis

Hideto Yoshikawa, MD, and
Tokinari Abe, MD

A normally developed 12-year-old female drank a cup of tea and could not sleep that night. The next morning, symptoms suggestive of parkinsonism developed, including progressive rigidity, akinesia, and a mask-like face. These signs lasted for 10 days. Brain computed tomography revealed multiple calcification, and thus she was diagnosed as having bilateral striopallidodentate calcinosis. Patients with bilateral striopallidodentate calcinosis exhibit various movement disorders. However, there have been no reports of transient parkinsonism associated with bilateral striopallidodentate calcinosis, including in children. **© 2003 by Elsevier Inc. All rights reserved.**

Yoshikawa H, Abe T. Transient parkinsonism in bilateral striopallidodentate calcinosis. Pediatr Neurol 2003;29: 75-77.

Introduction

Although idiopathic cerebral multiple calcification including of the basal ganglia, thalamus, dentate nucleus, and white matter has various names, such as Fahr's disease and familial idiopathic cerebral calcification, bilateral striopallidodentate calcinosis (BSPDC) is most descriptive [1]. The mechanism of calcification remains unknown. Some patients with BSPDC are asymptomatic, and others describe movement disorder caused by basal ganglia lesions. Psychiatric abnormalities are also common in BSPDC. In general, a patient with BSPDC is asymptomatic in the first and second decades of life, the neurologic features develop in the third decade of life, and thereafter deterioration occurs [1,2]. There has been no report of children with BSPDC indicating transient parkinsonism.

Case Report

This 12-year-old, normally developed Asian female graduated from elementary school and became emotionally unstable. Two days after, she went to a restaurant with her family, including her older sister, for a graduation celebration party and drank a cup of tea for the first time there. On that night she could not sleep. Next morning, she developed bradykinesia, rigidity, and gait difficulty without resting tremor. Pyrexia was not present. Other family members who drank a cup of the same tea developed no signs. These impairments gradually worsened and 2 days after the onset of her signs, in the morning, she became totally inactive and rigid, could not speak, and her facial appearance became apathic. She could not stand or walk. Thus she was admitted to our hospital.

On admission, physical examination disclosed no abnormal findings. Neurologic examination revealed cogwheel rigidity of the extremities, and increased deep tendon reflexes. Her symptoms suggested parkinsonism, including progressive rigidity, akinesia, a mask-like face, and dysphagia. Routine laboratory examinations including serum calcium and phosphorous revealed no abnormal findings. Other laboratory examination data including those regarding parathyroid hormone, various virus titers, auto-antibodies, amino acid analysis, organic acid analysis, lactate, pyruvate, copper, ceruloplasmin, and chromosomal analysis were normal. Cerebrospinal fluid examination disclosed cell count 1/3 μl, protein 28 mg/dL, glucose 68 mg/dL, lactate 11 mg/dL, pyruvate 0.7 mg/dL, and negative viral titers for measles, herpes simplex virus type 1, and cytomegalovirus. She also demonstrated a normal response to the Ellsworth Howard test, which is a parathyroid hormone loading test to exclude pseudo-hypoparathyroidism. Electroencephalography revealed no abnormal findings. Brain CT indicated multiple areas of calcifications in the dentate nucleus, thalamus, globus pallidus, putamen, caudate nucleus, and subcortical white matter, and an isolated cyst in the left frontal centrum semiovale (Fig. 1 A, B). MRI documented hyperintense lesions in the white matter, especially the centrum semi-

From the Department of Pediatrics, Niigata City General Hospital, Niigata, Japan

Communications should be addressed to:
Dr. Yoshikawa; Department of Pediatrics; Niigata City General Hospital; 2-6-1 Shichikuyama; Niigata 950-8739, Japan.
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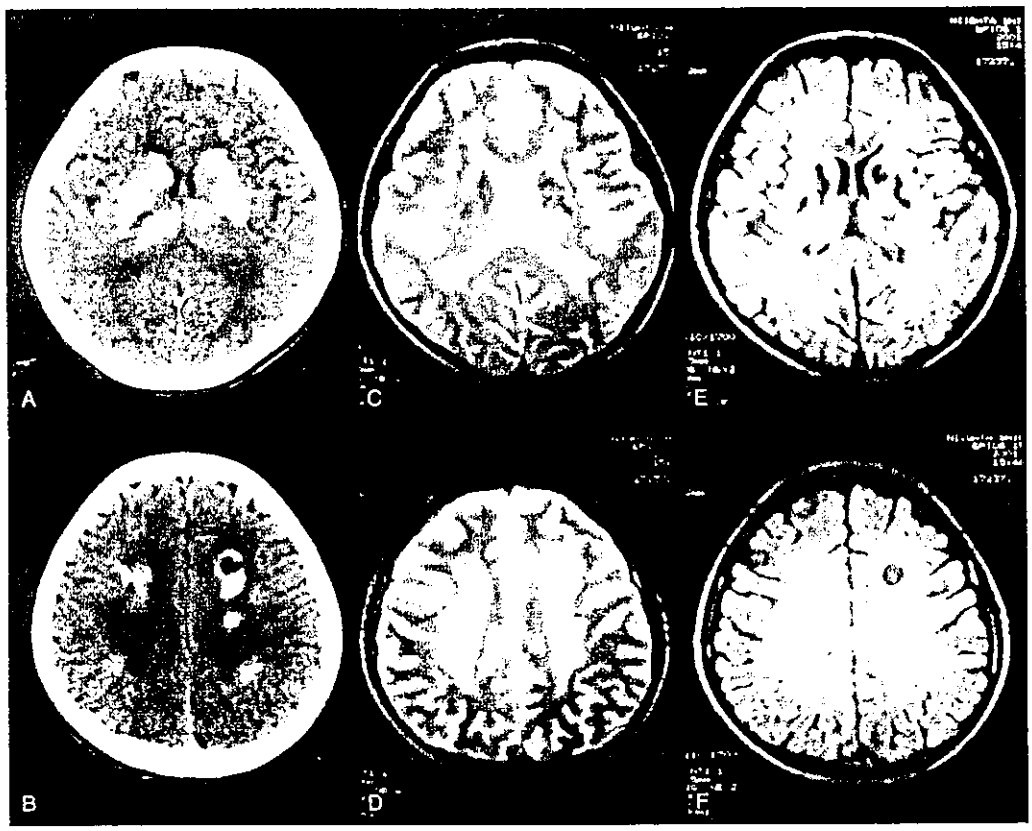

Figure 1. Brain CT and MRI findings. Brain CT (A, B) disclosed multiple calcifications and an isolated cystic lesion in the left frontal region. Low or null signals were observed in T_1, T_2 and FLAIR images of the areas in which calcification had been demonstrated on CT. High signals were seen in entire centrum semiovale, the white matter surrounding the lateral ventricles, and the left thalamic lesion in the T_2 and FLAIR images, in which no lesion had been demonstrated on CT. A, B: Brain CT. C, D: T_2-weighted images (TR 3600 ms/TE 110 ms). E, F: Fluid attenuation inversion recovery (FLAIR) method (TR 6650 ms/TE 110 ms).

ovale, apart from calcification, with T_2-weighted imaging and the fluid attenuation inversion recovery (FLAIR) method (Fig. 1 C, D, E, F). Cerebral angiography revealed no abnormal findings. Single photon emission tomography with ^{99m}Tc-ethyl-cysteinate-dimer (ECD) demonstrated decreased perfusion in the basal ganglia lesion. No other specific etiology was proven, but brain CT of her older sister with no findings documented similar multiple calcifications, which were milder than those of this patient. Although her BSPDC was familial, her parents did not want to undergo brain CT, and thus the inheritance pattern remained unclear. Therefore, she was diagnosed as having BSPDC. After admission, her extrapyramidal signs gradually worsened, and she became completely akinetic, could not swallow, and spontaneous urination was impossible. She required tube feeding and urination induction. After the 6th day following the onset of her abnormalities, the extrapyramidal signs gradually resolved spontaneously and by the 10th day they had disappeared completely. However, she still demonstrated some psychiatric findings, such as cognitive impairment, depression, and disorientation. The oral administration of clonazepam improved these psychiatric findings until the 27th day, and thus she was discharged. Thereafter, for 20 months she has been asymptomatic.

Discussion

BSPDC is an extremely rare disorder, especially in children, and it is hard to diagnose BSPDC in the first or second decade of life without neuro-imaging or an evident family history, because a patient with BSPDC usually does not reveal any signs despite multiple calcification until the third decade of life [1,2]. The basal ganglia lesions in BSPDC might cause some movement disorders, including parkinsonism [1,2], paroxysmal dystonic choreoathetosis (PDC) [3,4], and other involuntary movements. Manyam et al. [1] reviewed 16 cases of BSPDC associated with parkinsonism, 6 of their patients and 10 reported in the literature. They were aged from 38 to 78 years old. Their parkinsonism was permanent and progressive even if it was mild. To the best of our knowledge, there has been no report of a 12-year-old girl with BSPDC indicating transient parkinsonism. At present, she is young, and her parkinsonism might be mild and transient. However, in the future, she will probably develop permanent and more

severe parkinsonism [1,2], and thus we need to consider the use of anti-Parkinson drugs to prevent parkinsonism.

PDC is another condition that should be considered as one of the differential diagnoses. Paroxysmal dyskinesia occurs at rest both spontaneously and following caffeine or alcohol consumption. Episodes last from minutes to hours and may occur several times a day, which is different from the case reported here. There have only been two reported cases of BSPDC associated with PDC; 41 and 75 years old, respectively [3,4]. Also, there has been no report of children with BSPDC exhibiting PDC. Fink et al. [5] proposed that nigrostriatal neurons in PDC patients exhibit either marginally deficient dopamine synthesis or excessive caffeine-induced dopamine release; and that following caffeine-induced dopamine release, PDC patients experience a period of dopamine deficiency, which could manifest as dystonia. Our patients' features are different from those of PDC, however, a similar mechanism might be involved, because both parkinsonism and PDC are basal ganglion disorders, and we believe that they are triggered by basal ganglion dysfunction caused by calcification. Although another etiology inducing transient parkinsonism is considered to be a drug-induced one and causative agents include phenothiazines, thioxanthenes, and butyrophenones, she had never taken these drugs. Her abnormalities might have been induced by dopamine deficiency in the nigrostriatal system, caused by caffeine, sleeplessness, and/or emotional uplift.

On the contrary, caffeine intake is associated with a significantly lower incidence of Parkinson's disease [6]. Other components of tea, including polyphenol, amino acids, and vitamins are unrelated to the incidence of Parkinson's disease. The neuroprotective property of a green tea component, polyphenol, has been demonstrated in a mouse model of Parkinson's disease [7]. So, the transient parkinsonism which developed in this patient could conceivably have not been caused directly by caffeine or other components of tea.

Avrahami et al. [8] reported MRI findings in BSPDC, such as T_2 hyperintense signals in the white matter, mainly involving the entire centrum semiovale, which did not correspond to any calcification. No correlation was found between T_2 white matter hyperintensity and parkinsonism in their study. These findings were very similar to our patient's MRI findings. They speculated that the T_2 hyperintense signals may have reflected a slowly progressive, metabolic, or inflammatory process in the brain, which subsequently became calcified and was probably responsible for the neurologic deficit observed. Ellie et al. [2] have also reported T_2 hyperintense white matter lesions. Concerning the cystic lesion in our patient, cerebral infarction may conceivably be considered a cause because pathologically calcium deposits are commonly present along small vessels and capillaries in BSPDC. Idiopathic nonarteriosclerotic cerebral calcification is another pathologic name for Fahr's disease. However, a cystic astrosytoma in a cerebellar hemisphere in Fahr's disease has been reported [9]. Although the relationship between Fahr's disease and astrocytomas is uncertain, we have to monitor this cystic lesion to exclude neoplasm.

Our patient represents the first reported childhood case of transient parkinsonism associated with BSPDC.

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16年度研究成果の刊行に関する一覧表及び、その刊行物

16年度 研究成果の刊行に関する一覧表

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	著者氏名	論文タイトル	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
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Lesch-Nyhan syndrome

和 Lesch-Nyhan 症候群
MIM 300322

皮膚症状	びらん，爪変化，舌変化
全身症状	精神遅滞，不随意運動，自損行為，自咬症
病因	先天性代謝異常症

○定義

1964年にLeschとNyhanが，小児期に精神遅滞，舞踏様アテトーゼ，自損行為，高尿酸血症を呈する遺伝性疾患を報告した[1]．これがLesch-Nyhan症候群である．欠損酵素はヒポキサンチン-グアニンホスホリボシルトランスフェラーゼ（hypoxanthine-guanine phosphoribosyltansferase；HGPRT）で，本酵素はプリン代謝でプリンの回収路においてヒポキサンチンとグアニンの回収および再利用に働く．本酵素欠損では，プリン *de novo* 合成系が亢進し，尿酸合成が増加する．

○病因，疫学

本症候群は伴性劣性遺伝を呈し，*HGPRT* 遺伝子は染色体Xq26.1に座位する．遺伝子異常は，点突然変異，挿入，欠失など家系ごとに異なり，多彩である[2]．本症候群の正確な頻度は不明である．

○臨床症状

生後3～6か月ころまでに筋緊張低下，哺乳異常，1歳ころには舞踏病様あるいはアテトーゼなどの不随意運動が現れ，漸次，痙性四肢麻痺を呈してくる．また，本症候群に特徴的な口唇，舌，手指などを激しく咬む自損行為は1～2歳ころから認められる．末期には口唇は薄く，ときに部分的に欠落し，舌も短く，歯肉も破れ歯牙が見えることもある（図1a）．また，手指の爪や爪と皮膚の接合部を咬み，びらん，抜爪から指の切断に至ることもある（図1b）．

年齢が進むと高尿酸血症による尿路結

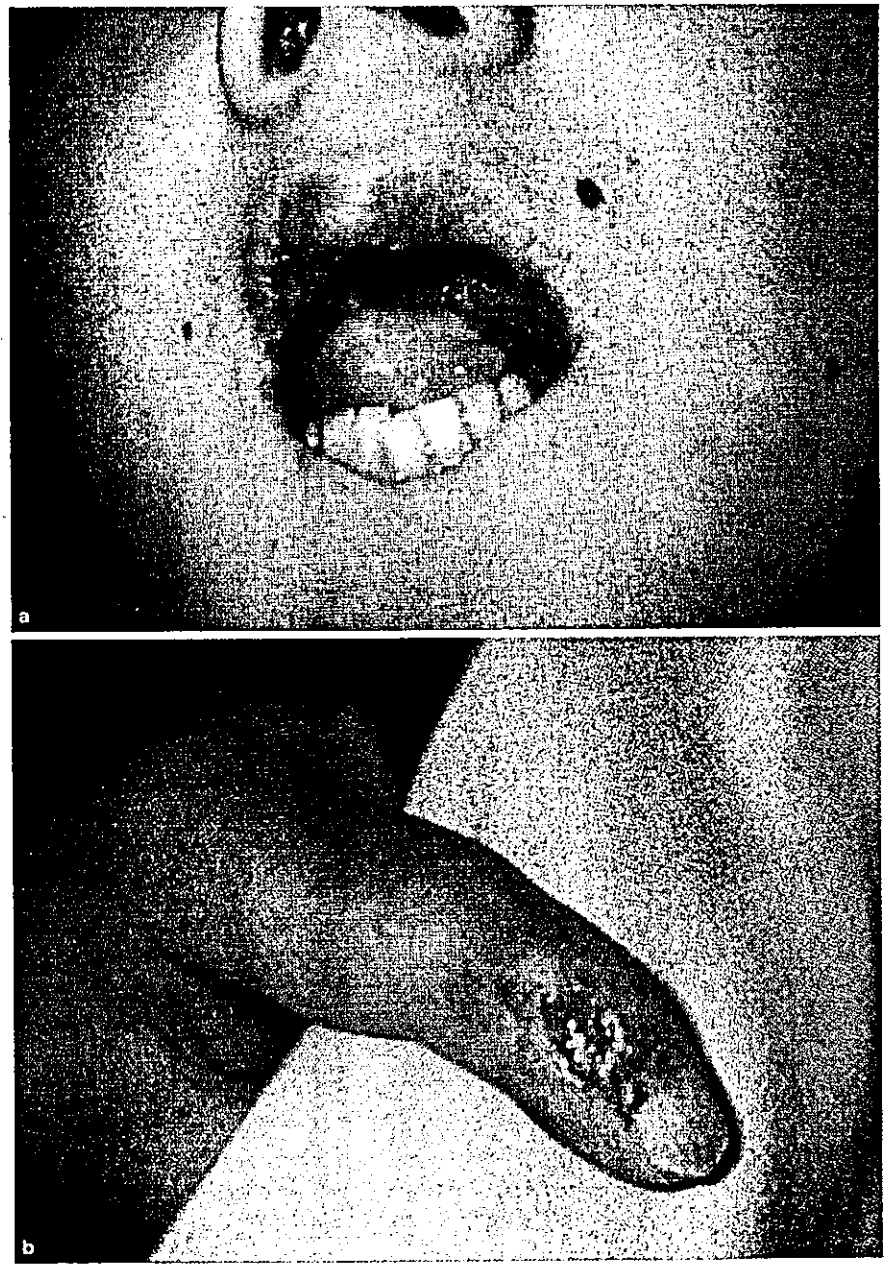

図1 Lesch-Nyhan症候群（14歳，男児）
a：自損行為により薄くなった下口唇．
b：自咬により傷ついた第2指．