Table 1. Perinatal characteristics and interventions for 60 live-born infants at GA 22–24 weeks

	2000–2004 (n = 32)	2005–2009 (n = 28)	p value
Obstetric characteristics			
CAM or p-PROM	16 (50)	17 (61)	0.28
Preeclampsia	2 (6)	6 (21)	0.09
Interventions			
Iatrogenic preterm delivery	8 (25)	8 (29)	0.49
Tocolytic treatment	30 (94)	15 (54)	<0.01
Antenatal steroid	2 (6)	9 (32)	0.01
Cesarean section	12 (38)	15 (54)	0.16
Neonatal interventions			
Intubation at birth	25 (78)	24 (86)	0.34
Surfactant administration	19 (59)	20 (71)	0.24

Figures in parentheses indicate percentages. CAM = Chorioamnionitis; p-PROM = preterm-premature rupture of membrane. Iatrogenic delivery means delivery was induced by maternal and/or fetal indications. Antenatal steroid therapy was defined as administration of any corticosteroid to the mothers between GA 22 and 34 weeks for accelerating fetal lung maturation.

Table 2. Neonatal characteristics and interventions of survivors born at 22–24 weeks of GA over one year

	2000–2004 (n = 14)	2005–2009 (n = 19)	p value
Neonatal characteristics			
Male sex	8 (57)	9 (47)	0.84
Multiple birth	1 (7)	2 (11)	0.74
1-min Apgar score <4	8 (57)	16 (84)	0.18
5-min Apgar score <4	3 (21)	8 (42)	0.38
SGA	0 (0)	6 (32)	0.06
GA <24 weeks	6 (43)	7 (37)	0.50
Birthweight <400 g	0 (0)	2 (11)	0.32
Interventions			
High-frequency oscillation	10 (71)	19 (100)	0.05
Indomethacin	7 (50)	17 (89)	0.03
Ligation	3 (21)	6 (32)	0.80
Early parenteral nutrition	5 (36)	18 (95)	<0.01
Transfusion	13 (93)	19 (100)	0.88

Figures in parentheses indicate percentages. Infants with body weight below the 10 percentile of the mean of the Japanese birth size standard data were classified as SGA. Indomethacin treatment was performed for the closure of PDA diagnosed clinically or by echocardiography.

age and then multiplying the quotient by 100. The mean and one standard deviation of DQ was 100.6 and 13.4, respectively. According to the protocol Japanese Society for Follow-up Study of High-Risk Infants, we defined as a normal or borderline developmental status a DQ score over 70, a mild status as a DQ from 50 to 70, and a moderate to severe status as a DQ less than 50 [12]. The study was approved by the Institutional Review Boards of Kyushu University.

Statistics

Differences between groups were tested for significance by the χ^2 test. Multivariate logistic regression analysis was conducted for survival over one year and normal to mild neurodevelopmental delay (DQ >50) as independent variables; dependent variables included perinatal characteristics, interventions and morbidities. Only dependent variables with a p value <0.25 on univariate analysis were entered into the multiple logistic models. The statistical analyses were conducted using Excel statistics (SSRI, Japan) for Windows and SPSS software (v19; SPSS, Chicago, Ill., USA). Results with p values <0.05 were considered significant.

Results

Survival of Infants Born at 22–24 Weeks of GA between 2000–2004 and 2005–2009

During the 10-year study period, a total of 82 infants were delivered at GA 22–24 weeks, including 42 in 2000–2004 and 40 in 2005–2009 (fig. 1). Ten and 12 of them were stillbirths or intrapartum deaths, and 32 and 28 were delivered as live-born infants in 2000–2004 and 2005–2009, respectively. In 2000–2004, 18 (56%) infants died within 365 days of life including 15 early (0–6 days) and 3 late (7–27 days) neonatal deaths, and 14 (44%) survived over one year. In 2005–2009, 9 (32%) infants died, including 7 early and 1 late neonatal death, and 19 (68%) survived to 1 year. This difference in survival rate is statistically significant (p = 0.04). When perinatal characteristics and interventions were compared, the 32 live-born infants in the second period underwent less frequently maternal tocolysis (54 vs. 94%, p < 0.01) and more frequently antenatal steroid therapy (32 vs. 6%, p = 0.01) than 28 born in the first period (table 1). No other profile differed significantly between the two groups (table 2).

Survival Factors for Infants Born at 22–24 Weeks of GA

When neonatal characteristics and interventions were compared between the 14 (in 2000–2004) and 19 (in 2005–2009) survivors, the post-2005 survivors received more frequently indomethacin therapy (89 vs. 50%, p = 0.03) and early parenteral nutrition (95 vs. 36%, p < 0.01) than the pre-2004 ones (table 2).

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Table 3. Clinical variables associated with a DQ >50 at 3 years of age

Variable	Infants born at 22–24 weeks of GA treated in NICU (n = 48[1])					
	univariate			multivariate		
	OR	95% CI	p value	OR	95% CI	p value
GA <24 weeks	0.19	0.05–0.67	0.02	0.14	0.03–0.67	0.01
Parenteral nutrition	4.82	1.38–16.76	0.02	1.01	0.09–10.78	0.99
Ligation	7.88	1.42–43.66	0.03	0.19	0.01–2.39	0.20
Transfusion	9.47	1.10–81.73	0.05	8.87	0.97–81.37	0.05
High-frequency oscillation	5.19	1.00–26.95	0.08	5.24	0.45–61.75	0.19
Indomethacin	2.43	0.74–7.98	0.24	9.75	0.67–141.9	0.10
1-min Apgar score <4	0.45	0.12–1.63	0.37			
Male sex	0.59	0.18–1.90	0.56			
Birthweight <400 g	3.29	0.28–39.16	0.70			
Iatrogenic preterm delivery	1.21	0.34–4.29	0.77			
5-min Apgar score <4	0.68	0.19–2.43	0.78			
Multiple birth	0.56	0.10–3.26	0.82			
SGA	1.17	0.23–5.94	0.85			
Cesarean section	1.11	0.35–3.54	0.86			
Tocolytic treatment	0.89	0.24–3.37	0.86			
Antenatal steroid	1.37	0.35–5.34	0.92			

OR = Odds ratio; CI = confidence interval. Logistic regression analysis was used to investigate the independent variables on a DQ >50. Obstetric characteristics and interventions, neonatal characteristics and interventions with a p value <0.25 on univariate analysis were entered into the multivariate logistic models.

[1] Three patients in whom neurodevelopmental status was not evaluated were excluded.

Neurological Morbidity of Survivors Born at *22–24 Weeks of GA at 3 Years of Age*

Three patients (1 in the first and 2 in the second period) were not evaluated because of moving or being treated for malignancy. Seven (54%) of 13 evaluable survivors attained a normal or borderline developmental status (DQ >70) in 2000–2004, and 7 (41%) of 17 survivors obtained that level in 2005–2009. Four (31%) infants in the pre-2004 group and 7 (41%) in the post-2005 group had a moderate or severe developmental delay (DQ <50). The proportion of infants who attained a DQ >50 did not reach statistical significance in the first and the second study period (69 vs. 59%, p = 0.84).

Neurodevelopmental Factors for Attaining a DQ >50 at 3 Years of Age

The attainment of a DQ >50 in survivors at 3 years of age was negatively associated with GA <24 weeks (p = 0.02), and positively associated with ductus ligation (p = 0.02) and parenteral nutrition (p = 0.03) when assessed by univariate analysis. Multivariate analysis indicated a significant association only with GA <24 weeks (p = 0.01; table 3).

Discussion

The survival rate of infants born at GA 22–24 weeks increased significantly from 52 to 79% in a tertiary center during the decade studied. In addition, the percentage of SGA increased from 0 to 32% between the two periods. The improved survival might be due to the prenatal management including the restraint of tocolytic treatment and the more extensive use of antenatal steroid therapy, as well as to the neonatal management such as the promotion of indomethacin treatment and parenteral nutrition. However, at 3 years of age survivors born in 2005–2009 did not attain a more favorable neurodevelopment than those born in 2000–2004. The premature birth at GA <24 weeks was the most critical factor influencing neurodevelopment in survivors.

Antenatal steroid therapy has been reported to decrease the mortality of infants with GA 22–25 weeks [7, 13]. Prophylactic indomethacin may have short-term benefits for preterm infants including a reduction in the incidence of symptomatic PDA, PDA surgical ligation, and severe IVH [14]. From 2006, we routinely introduced indomethacin prophylaxis for preterm infants born at

<25 weeks of GA to reduce the risk of intraventricular hemorrhage. However, the timing of administration varied with the clinical condition of patients or individual physician preference. The nutritional problems of preterm infants have become particularly relevant to survival from NICU, as numerous studies have underlined the importance of parenteral nutrition for short- and long-term neurodevelopmental outcomes. The post-2005 survivors received more high-frequency oscillation therapy (71 vs. 100%, p = 0.05) than the pre-2004 ones. However, it is controversial to what extent indomethacin, parenteral nutrition and high-frequency oscillation could affect the mortality of these infants [15].

In the present study, although the survival of preterm infants at the limit of viability increased significantly over a decade, the neurodevelopment of the survivors (DQ >50), did not improve, and actually it deteriorated from 69 to 59%. However, since the total number of survivors who attained a borderline or normal development (DQ >70) was small, this trend did not reach statistical significance or was it possible to evaluate it with a multivariate analysis. We did not have enough infants in our single institute to evaluate survival and neurodevelopmental outcome at GA 22, 23 and 24 weeks. There are a few reports on the neurological outcome of survivors at GA 22 weeks [6, 16]. The cohort study of the Neonatal Research Network, Japan, revealed that the proportion of unimpaired or minimally impaired was 12.0% at GA 22 weeks and 20.0% at GA 23 weeks [17]. Infants born at GA 22–25 weeks are fragile and vulnerable to medical interventions because of the extreme immaturity of organ systems. If the survival rate increases and the neurodevelopmental impairment remains the same, the absolute number of infants with neurological problems will increase. However, the guideline for resuscitation of preterm infants at the limit of viability is still used in Japan. Based on the presented data, the probability of not only survival but also neurodevelopmental outcome of these infants is vital for counseling parents, informing care, and planning service. Recently, a prospective follow-up study of very low-birthweight infants in Japan has revealed that periventricular leukomalacia, gastrointestinal perforation, intraventricular hemorrhage, and moderate or severe bronchopulmonary dysplasia correlated with the developmental delay at 3 years of age [12]. Brain development occurs actively during the second and third trimesters of fetal life, with neurogenesis, neural migration, maturation, apoptosis, and synaptogenesis [18, 19]. Repeated courses of antenatal steroids have a promoting effect on the myelination in developing nonhuman primate brain [20]. Further studies are required to explore the significant association of antenatal steroids with long-term neurodevelopmental outcome in the light of their possible neuroprotective effects.

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Case report

Staphylococcal endocarditis as the first manifestation of heritable protein S deficiency in childhood

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abstract

A 12-year-old Japanese girl developed infective endocarditis and central nervous system disease. The previously healthy girl showed altered consciousness and abnormal behaviors along with the classical signs of septic emboli. Staphylococcus aureus was isolated from peripheral blood, but not, the pleocytotic cerebrospinal fluid. Diagnostic imaging studies revealed a vegetative structure in the morphologically normal heart, and multiple thromboembolisms in the brain and spleen. Low plasma activity of protein S (12%) and thrombophilic family history allowed the genetic study, demonstrating that she carried a heterozygous mutation of PROS1 (exon 13; 1689C > T, p.R474C). Surgical intervention of the thrombotic fibrous organization and subsequent anticoagulant therapy successfully managed the disease. There are no reports of infective endocarditis in childhood occurring as the first presentation of heritable thrombophilia. Protein S deficiency might be a risk factor for the development or exacerbation of infective endocarditis in children having no pre-existing heart disease.

1. Introduction

Infective endocarditis (IE) is an infection of the mural endocardium caused by various bacteria or fungi. It rarely occurs in children presenting with vegetations, septic emboli, valve damages, and heart failure [1]. The majority of patients have underlying conditions such as rheumatic valvulopathy or congenital heart disease (CHD) [2]. Antibiotic managements controlled rheumatic heart diseases, and appreciably reduced the IE-risk in patients with unrepaired CHD. However, the incidence of pediatric IE is still increasing [2,3]. Advances in the cardiac surgery improved the survival rate of CHD patients, and might increase the number of IE-risk patients harboring bioprosthetic and synthetic devices. Recent reports delineated a continuing shift in the epidemiology of pediatric IE toward a proportion of children without pre-existing heart disease [3,4]. The shift accounts for the growing numbers of preterm infants and children who need indwelling central venous catheters for the management. On the other hand, there is little information about the etiology of IE occurring in previously healthy children who have no structural heart disease.

Protein S (PS) deficiency is one of the genetic traits predisposing persons to hypercoagulability [5]. Homozygous PROS1 mutation leads to fetal loss or, if any, neonatal purpura fulminans. Adult carriers of the heterozygous mutation are at high risk of stroke, pulmonary embolism, and deep vein thrombosis. PS deficiency can be acquired in vitamin K deficiency, warfarin or sex hormone therapy, pregnancy, liver disease, and infections. PS-deficient patients are prone to thromboembolic events during cardiac surgery. There are no reports of IE as the first manifestation of heritable thrombophilia.

We report herewith a pediatric case of PS-deficient heterozygote, beginning with an intractable IE and systemic thromboembolism in no pre-existing heart disease.

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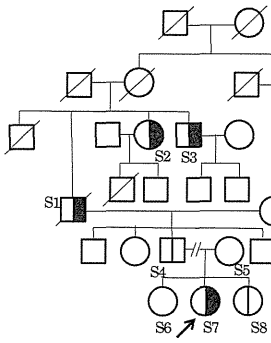
2. Case report

A 12-year-old Japanese girl was transferred to our hospital for the treatment of IE and central nervous system (CNS) disease of unknown etiology. The patient with no previous illness developed headache and vomiting. The next day (the 2nd day of illness), she showed fever and disturbed consciousness. On the 3rd day of illness, the patient was admitted to our affiliated hospital because CNS infection was suspected. Peripheral blood studies showed a leukocyte count of 16.09 × 10^9/L and C-reactive protein (CRP) of 16.18 mg/dl. Cerebrospinal fluid (CSF) analysis revealed a cell count of 54/ml with 46% polymorphonuclear cells and 54% lymphocytes, glucose of 85 mg/dl, and protein of 32.2 mg/dl. Methicillin-sensitive Staphylococcus aureus (MSSA) was isolated from the peripheral blood but not CSF cultures. Electroencephalogram revealed diffuse slow wave. Cefotaxime, panipenem/betamipron and acyclovir were intravenously started for the treatment of meningoencephalitis. Because of the thrombophilic family history and an abnormal structure in the left ventricle assessed by echocardiography, she was referred to our hospital at the 5th day of illness.

On admission, an afebrile well-nourished girl showed a pulse rate of 56 beats/min, a respiratory rate of 22 breaths/min and a blood pressure of 110/59 mmHg. The patient was listless but showed no meningeal signs. The Glasgow Coma Scale was E4V5M6. Auscultations revealed normal heart and respiratory sounds. There was no hepatosplenomegaly. Splinter hemorrhage and non-tender petechiae were found on the toes. Roth spots were determined on the retina. Complete blood cell counts showed a leukocyte count of 10.59 × 10^9/L with 83.5% segmented neutrophils, a hemoglobin concentration of 12.3 g/dl and a platelet count of 185 × 10^9/L. Liver and kidney functions were normal. CRP concentration was 7.45 mg/dl. Serum brain natriuretic peptide levels were elevated [51.3 pg/mL; reference range (rr): 0e18.4]. Coagulation studies revealed normal ranges of fibrinogen 321 mg/dl, prothrombin time (PT%) 78% and activated partial thromboplastin time 32.5 s (rr: 26e41), and slightly increased levels of fibrinogen degradation products 5.4 mg/ml (rr: <5.0), D-dimer 2.0 mg/ml (rr: <0.5), thrombin-antithrombin complex 3.7 ng/ml (rr: <3.0), and plasmin a2-antiplasmin complex 1.2 mg/ml (rr: <0.8). Plasma anticoagulant activities showed low PS of 12% (rr: 59e128), subnormal protein C (PC) of 66% (rr: 75e131), and normal antithrombin of 103% (rr: 80e120). Protein induced by vitamin K absence/antagonist-II was undetectable. Normal PS antigen levels (69% rr: 65e135) and free-PS antigen levels (36% rr: 60e150) favored the diagnosis of type III PS deficiency. Detailed family history disclosed that two siblings of the paternal grandfather were diagnosed as having PS deficiency because of mesenteric artery thrombosis and pulmonary infarction in their fifties. Asymptomatic father and younger sister of the patient had low PS activity (Fig. 1).

Venous blood cultures yielded MSSA. Sterile CSF showed a cell count of 98/ml with 88% polymorphonuclear leukocytes and 12% lymphocytes, glucose of 99 mg/dl, and protein of 21.0 mg/dl. Transesophageal echocardiography revealed a vegetative structure (13 × 5 mm) in the left ventricular outflow tract. Head magnetic resonance imaging showed multiple white matter lesions with high signal intensity of T1-weighted fluid-attenuated inversion recovery and diffusion weighted image (DWI) on the splenium of corpus callosum and frontal and parietal lobes, indicating cerebral venous infarction. These determined the diagnosis of IE and cerebral infarctions associated with PS deficiency. Cefazolin (CEZ) and gentamicin (GM) therapy led to a partial resolution of symptoms but not vegetative mass. Because of the flare of fever and peripheral thrombotic lesions, the intraventricular lesion was removed by cardiac surgery on the 26th day of illness. The pedunculated structure located on the left ventricle wall adjacent to left coronary cusp, containing organizing thrombi with granulation tissue, but not mesenchymal cells or bacterial colonies (Fig. 2). Antimicrobial (CEZ + GM) and anticoagulant therapy (aspirin + warfarin following heparinization) was then started. After the stop of antimicrobial agents at the 50th day of illness, she is alive and well on warfarin therapy. The genetic study demonstrated that the patient was a heterozygous carrier of the reported mutation in exon 13 of PROS1 (1689C> T, Arg474Cys) [6].



Subject	PS activity (%)	Free PS antigen (%)	Total PS antigen (%)
S4	19	36	65
S5	69	68	70
S6	70	79	67
S7	12	36	69
S8	22	33	28

Fig. 1. Family pedigree of the present patient (arrow), and plasma protein S (PS) activity, free PS antigen, and total PS antigen in Subjects 4e8 (table). Subject 1 developed thromboembolisms in the leg at 49 years of age, cerebral infarction at 50 years, and mesenteric arterial thrombosis at 62 years. Subject 2 suffered from mesenteric arterial thrombosis at 59 years of age. Subject 3 had a history of pulmonary infarction. Subjects 4 (42 years old) and 8 (10 years old) had no history of thrombosis. Subjects 2 and 3 had been diagnosed as having PS deficiency. S: Subject.

3. Discussion

Associated conditions in IE children without preexisting heart disease include neoplasms, prematurity, connective tissue disorders, and diabetes mellitus [3]. However, inherited thrombophilia

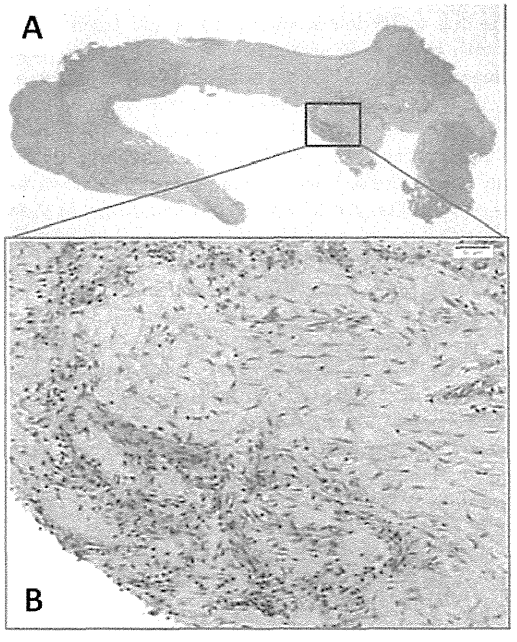


Fig. 2. Histological examination of a pedunculated structure on the left ventricle wall contained organizing thrombi with granulation tissue and fibrous tissue (Hematoxylin and eosin stain, original magnification A: × 40, B: × 400). There are edematous and myxoid changes, but no mesenchymal cells or bacterial colonies were observed.

had not been recognized a risk of IE. Lin et al. [4] characterized the feature of IE in non-CHD children; prevalent infection of S. aureus (MRSA and MSSA), vegetations in the right-sided heart, older age, and higher requirement of surgical intervention. Although the present patient later disclosed an episode of deciduous tooth loss two weeks prior to the onset of disease, the contribution remains unknown to the development of staphylococcal IE. The pathological findings of the intracardiac mass might be suggestive for nonbacterial thrombotic endocarditis (NBTE), arising in association with primary antiphospholipid syndrome, myeloproliferative disorders and malignancy [7]. On the other hand, granulation in the lesion, not usually observed in NBTE, indicated the presence of inflammation. Absent mesenchymal cells precluded the diagnosis of myxomatous tumor. The present case fulfilled the clinical criteria of IE, although S. aureus was identified from blood culture one time only. Furthermore, cerebral infarction, the most serious extracardiac complication of two different types of endocarditis, did not recur on anticoagulant therapy after the surgical intervention. These observations suggested that the predisposition of hypercoagulability could precipitate the formation of intra-ventricular clot with certain triggers such as occult bacteremia, and resulted in the intractable IE. Even if IE occurred in chance association with PS deficiency, it is not to say exaggerated that thrombophilia was one of the exacerbating factors of IE.

The major concern is the location of the vegetative lesion; why did it originate from the out-flow tract of left ventricle, but not, of right one in this patient? There are many reported cases of PS-deficient patients who developed arterial thromboembolism including stroke and mesenteric artery thrombosis. PS-deficient children might have a potential risk of arterial thrombosis [8]. Nevertheless, the association of heterozygous PS deficiency with venous but not arterial thrombosis is proven [9]. Girolami et al. [10] reported a 31-year-old man who developed both left and right atrial thrombosis, as presenting symptom of heritable PS deficiency. Obic et al. [11] described a 77-year-old woman with unremarkable medical history who had native aortic valve thrombosis associated with PS deficiency. Maldjian et al. [12] reported that a previously healthy 39-year-old woman developed intracardiac thrombus due to PS-deficiency. On the other hand, no pediatric patient with isolated PS deficiency was reported to suffer from intracardiac thrombosis. Paç et al. [13] reported a case of biventricular cardiac thrombi in a 3-year old-girl with PC and PS deficiencies after the treatment of urinary tract infection and pneumonia. Mattiau et al. [14] described a 2-year-old girl with PC deficiency who presented with thrombus in the left ventricle and systemic emboli after the treatment of pneumonia. In these cases, intracardiac thrombi occurred in association with infection, but not limited to either-sided heart. To the best of our knowledge, there is only one case having a large vegetation of IE and PS deficiency [15]. The clinical course of the 81-year-old woman with no pre-existing heart disease was progressive. Taken together, surgical intervention must be inevitable for the treatment of thrombophilic IE patient, irrespective of the location of vegetative lesions.

The most prevalent form of heritable thrombophilia in Japan is PS deficiency, because of the polymorphism of PS-tokushima [16]. However, the mutation carriers are considerably found in the series of deep vein thrombosis [6,16]. The patient's pedigree disclosed the segregation of thrombophilic patient and PS deficiency. Secondary decrease of plasma PS activity in infection makes it difficult to diagnose heterozygous PS deficiency. The management of infection-associated hypercoagulability in such mutant carriers should be individualized according to the types of thrombophilia. Further study is needed to determine whether heritable thrombophilia is a risk factor for the development of IE in previously healthy non-CHD children. However, we should pay more attention to heritable thrombophilia in the management of pediatric IE.

Conflicts of interest

The authors state that they have no conflicts of interest.

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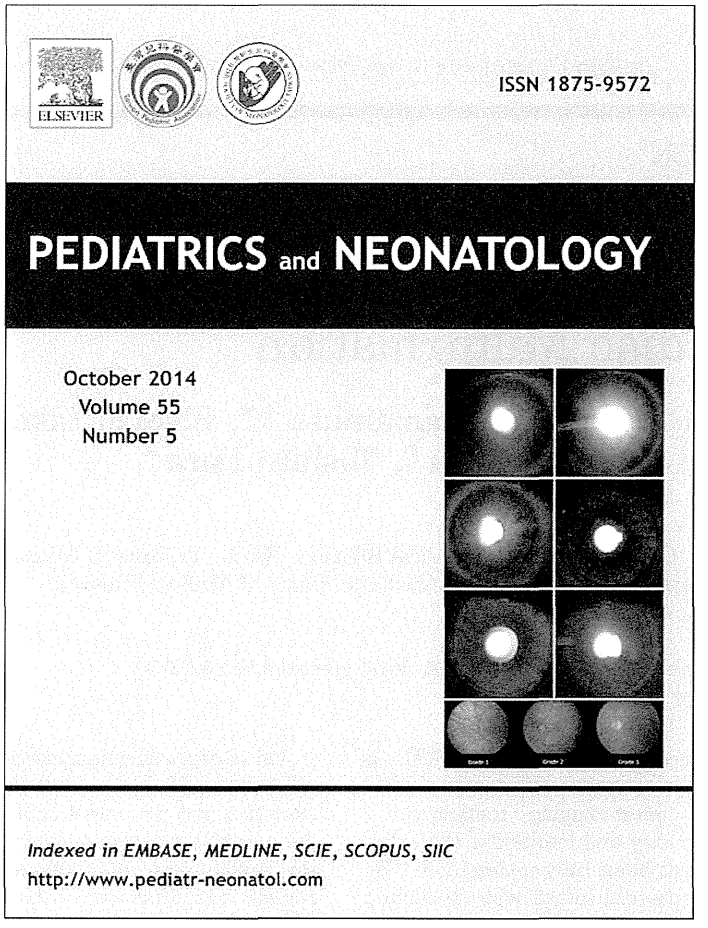

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BRIEF COMMUNICATION

Tachyarrhythmia-induced Cerebral Sinovenous Thrombosis in a Neonate Without Cardiac Malformation

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Neonatal cerebral sinovenous thrombosis (CSVT) is becoming increasingly diagnosed because of greater clinical awareness and improved neuroimaging techniques.[1,2] Despite the substantial mortality and morbidity, the etiology of pediatric CSVT has not been fully understood.[3] We herein report a case of 13-day-old infant who developed intractable paroxysmal supraventricular tachycardia, which was subsequently complicated with CSVT.

A 13-day-old Japanese male was admitted to our affiliated hospital because of poor feeding and not doing well for 2 days. The infant was delivered at term with a birth weight of 3458 g and full APGAR scores. There was no cardiomyopathy or prothrombotic disorder in his relatives. On admission, he presented tachycardia at 300 beats/minute with hypotension. The electrocardiogram (ECG) showed narrow QRS tachycardia with following P wave suggesting the diagnosis of paroxysmal supraventricular tachycardia (Supplementary Figure 1). Cardioversion (0.5 J/kg twice) after the intubation allowed restoration of a sinus rhythm. The patient was then transferred to our hospital for intensive treatment.

Initial physical examination demonstrated an afebrile and pale infant. He had a sinus rhythm but presented cold extremities and prolonged capillary refill time (>3 seconds). Auscultation revealed a gallop rhythm of the heart. Chest X-ray examination demonstrated pulmonary congestion and cardiac dilatation with a cardiothoracic ratio of 61% The echocardiogram demonstrated an impaired left ventricular function with ejection fraction at the level of 50% Laboratory examinations are as follows: white blood cell count 10.68×10^9/L; hematocrit 35.7% platelet count 157×10^9/L; creatinine kinase 342 U/L; creatine kinase-MB 71 U/L; lactate dehydrogenase 601 U/L; C-reactive protein 0.11 mg/dL; troponin-T 0.154 ng/mL; prothrombin timee international normalized ratio 1.62; activated partial thromboplastin time 40.1 seconds; fibrinogen degradation products 63.1 ng/ml; D-dimer 28.5 ng/mL; and brain natriuretic peptide 3956 pg/mL.

The ECG during tachycardia documented the characteristics of atrioventricular reentrant tachycardia at 300 beats/minute. The tachycardia was terminated by the intravenous rapid infusion of ATP three times. The ECG during sinus rhythm showed no delta wave, suggesting the possibility of concealed WPW syndrome. Oral propranolol (1e 2 mg/kg/day) and flecainide (3e 6 mg/kg/day) succeeded to prevent the recurrence of refractory arrhythmia. The echocardiogram showed a smooth recovery of the left ventricular function to the normal level of 63%2 days after admission.

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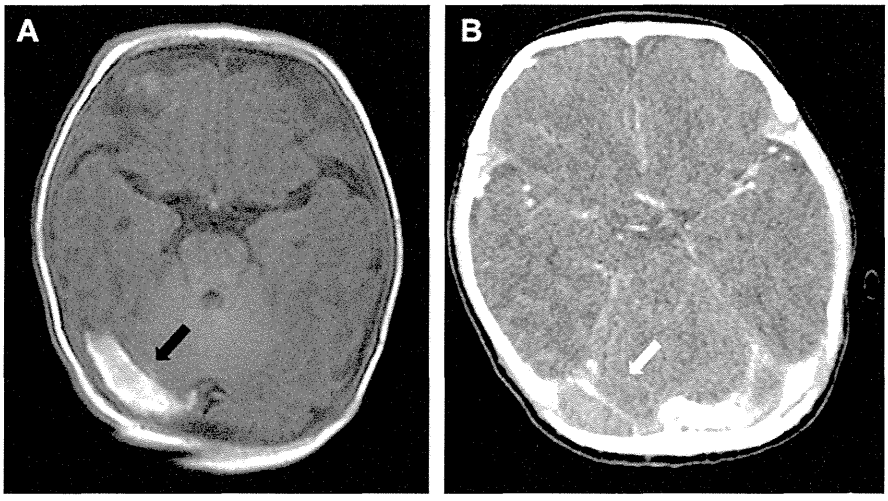

Figure 1 (A) T1-weighted magnetic resonance imaging. (B) Contrast-enhanced computed tomography of the brain after restoration of sinus rhythm. High signal intensity on T1-weighted magnetic resonance imaging (arrow) and flow disturbance on computed tomography (white arrow) confirmed the diagnosis of right transverse sinus thrombosis.

Magnetic resonance imaging (MRI) was performed 9 days after admission, in order to assess the cerebral damage due to cardiogenic shock. CSVT was indicated on MRI findings (Figure 1A). Computed tomography (CT) of the brain determined a right transverse sinus thrombosis (Figure 1B). Continuous infusion of fractionated heparin (10e 22 unit/kg/hour, activated partial thromboplastin time 42e 50 seconds) was started. Two weeks after the anticoagulant therapy, CT demonstrated recanalization of the transverse sinus. There were no laboratory data indicating inherited or acquired thrombophilic predispositions (on 12 days after admission): normal plasma activity of protein C 69%, protein S 58% and antithrombin 91% and undetectable titer of anticardiolipin antibody 2 U/mL. The patient received no additional anticoagulant therapy. CSVT did not recur for 6 months after the first event.

This is the first report of neonatal CSVT as a complication of paroxysmal supraventricular tachycardia. Perinatal complications, dehydration, sepsis, meningitis, and inherited thrombophilias such as antithrombin, protein C, or protein S deficiency are the major associations with pediatric CSVT.[4,5] A recent case series reported that none of the neonates with CSVT had persistently low activity of protein C, protein S, or antithrombin, and some of them were considered to have acquired prothrombotic states.[4] This patient showed no evidence of prothrombotic disorders, although FD fibrinogen degradation products P and D-dimer had already been elevated on admission. Pediatric venous thrombosis occurs at the highest incidence in neonates. Extremely high brain natriuretic peptide level suggested the presence of cardiac deterioration due to prolonged tachycardia. We speculate that the cardiogenic shock led to the stasis of cerebral sinus venous flow that predisposed the neonate to developing thrombosis.

No randomized clinical trials have been conducted concerning anticoagulation therapy for neonatal CSVT. However, the American College of Chest Physicians recommended initial anticoagulation except in the presence of significant hemorrhage.[6] The favorable response to the short-term anticoagulant therapy in the present case might corroborate that CSVT was not associated with inherited coagulopathy, but the transient circulatory disturbance.

Because the symptoms of CSVT are nonspecific, and often subtle or asymptomatic, the diagnosis is delayed and may be missed altogether. Our patient did not present any neurological symptom at the diagnosis of CSVT. Intensive imaging tests including brain echogram, CT, and MRI, and appropriate anticoagulant therapy should be considered for the neonates having sustained tachyarrhythmia with cardiac failure.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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Angelman 症候群の患児に多数歯齲蝕を認めた 1 例

山座治義[1]　増田啓次[2]　柳田憲一[2]
西垣奏一郎[1]　小笠原貴子[2]　廣藤雄太[1]
野中和明[1]

要旨：Angelman 症候群は，第 15 番染色体長腕 q11.2–q13 領域に存在する *UBE3A* を責任遺伝子とする遺伝性疾患である。本疾患は，生後 6～12 か月ごろより精神遅滞，運動失調など多様な中枢神経症状を示すようになる。我々は，多数の乳歯齲蝕を伴う Angelman 症候群の 1 例を経験したので報告する。

患児は，当科初診時年齢 1 歳 6 か月の男児で，精神遅滞，特異的顔貌として尖ったおとがい，脳波検査における高振幅の不規則徐波の出現，第 15 番染色体長腕 q11–q13 領域のヘテロ欠失などの所見から当院小児科にて Angelman 症候群と診断され加療を受けていた。口腔内所見として，視診・触診にて多数歯に及ぶ齲蝕が疑われた。しかし，重度の精神遅滞に加えて低年齢であったことから，覚醒下では十分な検査と治療ができないと判断し，保護者の同意を得て全身麻酔下での齲蝕治療を施行した。麻酔中の呼吸・循環動態は安定に経過し，治療後の合併症もなく処置翌日に当院小児科を退院した。Angelman 症候群の歯科口腔領域の特徴として，下顎前突や舌の肥大化，歯間分離，永久歯のエナメル質減形成が報告されている。当院小児科とも連携しながら，定期的な口腔衛生指導を行っていく方針である。

Key words：Angelman 症候群，UBE3A 遺伝子，ゲノムインプリンティング，齲蝕

緒　言

Angelman 症候群（以下，AS と略す，OMIM 105830）は，英国の Harry Angelman により，共通の特徴的症状を有する 3 人の子供について 1965 年に初めて報告された遺伝性疾患である[1]。主症状として，重度精神遅滞，運動失調，てんかん，容易に誘発される笑い，特異的顔貌などがあり，発生頻度は 10,000～20,000 人に 1 人の割合とされている[2]。本疾患の責任遺伝子は *UBE3A* であり，第 15 番染色体長腕 q11.2–q13 領域に存在する[3]。この領域の遺伝子の多くはゲノムインプリンティングによる発現調節を受ける[4]。*UBE3A* の場合，脳組織では母親由来 *UBE3A* のみが発現し父親由来 *UBE3A* は不活化されている[4]。したがって，何らかの要因で母親由来の *UBE3A* が機能喪失することにより中枢神経系を中心に症状が出現すると考えられている[5]。

我々は，多数歯齲蝕を伴う AS の 1 例を経験した。本症例の治療経過および歯科的問題点について考察を加えて報告する。なお，本症例の公表について保護者の承諾を得ている。

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（2014 年 5 月 23 日受付）
（2014 年 8 月 18 日受理）

症　例

患児：初診時年齢 1 歳 6 か月（男児）

主訴：齲蝕の精査・加療

現病歴：10 か月時，乳幼児健康診査にて独座ができなかったため，精査目的に当院小児科を紹介受診した。遠城寺式・乳幼児分析的発達検査では精神運動発達の遅延（7 か月程度）を認めた。さらに特異的顔貌として尖ったおとがい，脳波検査における高振幅の不規則徐波の出現，染色体検査にて第 15 番染色体長腕 q11–q13 領域のヘテロ欠失を認めたことなどから AS と診断された。1 歳 6 か月時，乳幼児健康診査にて齲蝕を指摘されたため，保護者が当院小児科主治医に相談したところ，当科受診を勧められ当科初診となった。

既往歴：AS

家族歴：特記事項なし（図 1）。

身体所見：初診時の身長は 83.4 cm（+0.9 SD），体重は 10.2 kg（−0.3 SD），Kaup 指数は 14.73（15 以上 19 未満が標準）であった。頚座と寝返りはできた。しかし，独座や独立歩行は不可能であった。頭部・顔貌所見として，扁平な後頭部，尖ったおとがい部，口唇周囲皮膚の

発赤とびらん，容易に引き起こされる笑いを認めた（図 2 a，b）。口腔内所見として，プラーク沈着が著明で口腔清掃状態は不良であった。舌や口腔粘膜などの軟組織に異常所見は認めなかった。歯牙所見として Hellman の歯年齢 IC 期で$\overline{B|B}$は萌出がなく$\overline{E+E}$は未萌出であった。上下顎ともに霊長空隙が認められ，乳犬歯の咬合関係は正常咬合であった。$\overline{A|A}$を除く他のすべての萌出歯に歯面の白濁もしくは実質欠損を認めた（図 2 c，d）。しかし，患児の協力が得られず視診・触診による口腔内診査は不十分でこれ以上の詳細については不明であった。

画像所見：頭部単純エックス線検査では$\overline{6E+E6}$歯胚が確認できた（図 3 a）。デンタルエックス線検査では患児の協力が得られず，写真は不鮮明となった。しかし，$\underline{DCBA|ABCD}$および$\overline{D|D}$に象牙質に達する透過像を認めた。$\overline{B|B}$の歯胚は確認できなかった（図 3 b）。

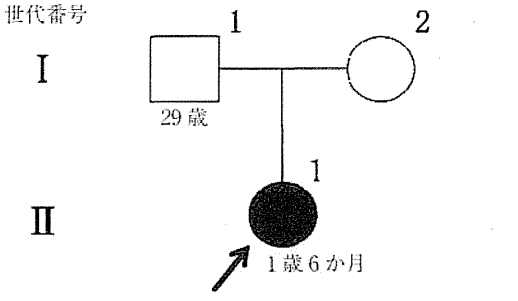


図 1　家系図（右肩の数字は各世代の個体番号を，矢印は発端者をそれぞれ示す）

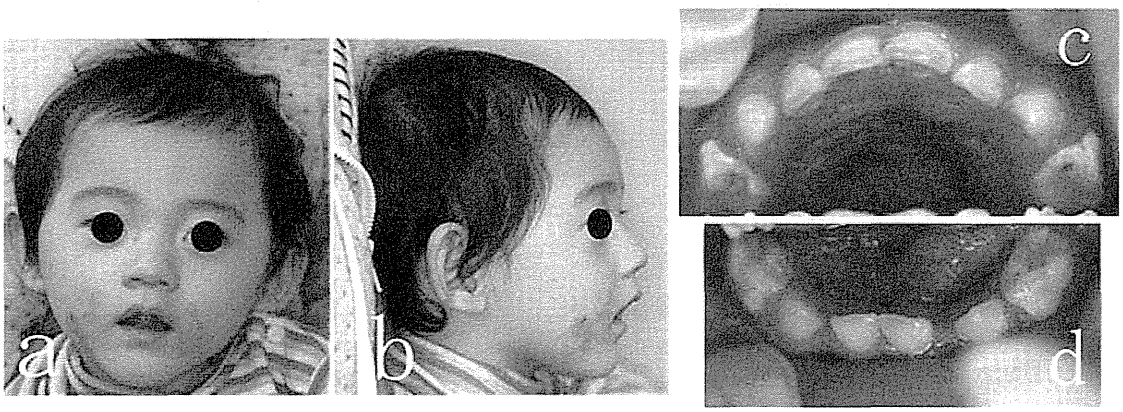


図 2　*GABRB3* 初診時写真
a．正貌　　b．側貌　　c．上顎歯列　　d．下顎歯列

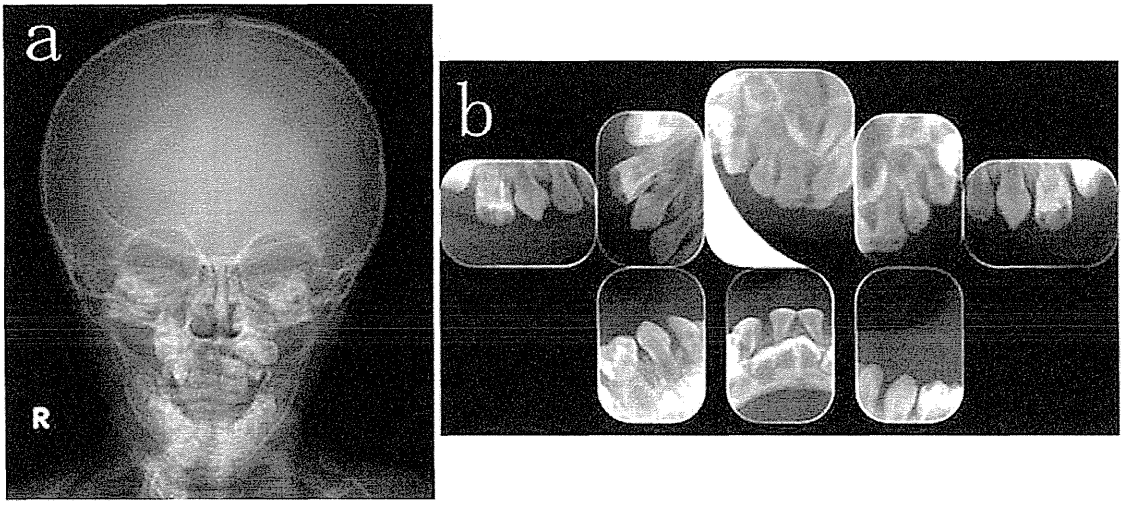
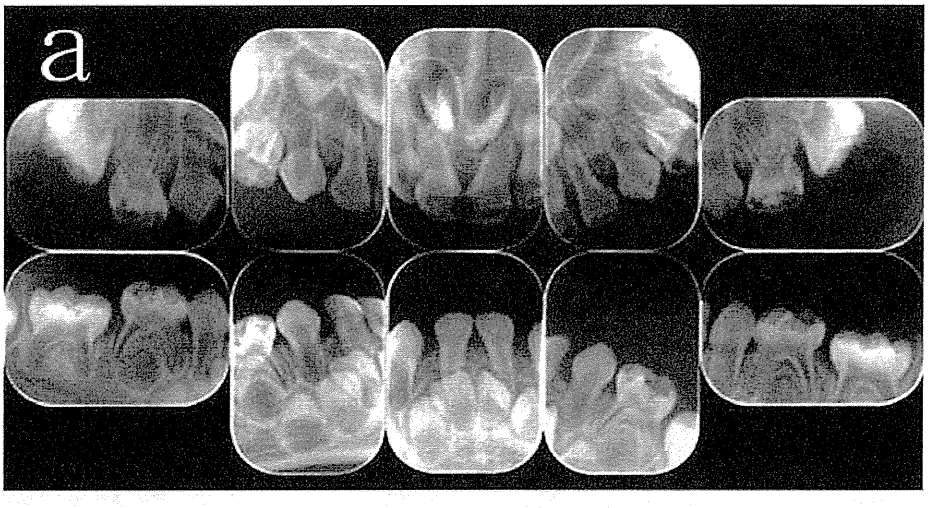


図 3　*GABRB3* 初診時エックス線写真
a．頭部単純エックス線写真　　b．デンタルエックス線写真

処置および経過

当院小児科主治医および歯科麻酔医と協議し，入院下で齲蝕の検査・診断を含めた全身麻酔下集中治療を行う方針とした。

治療当日朝，当院小児科病棟から手術室に入室した。酸素とセボフルランの混合ガス吸入にて緩徐導入し末梢静脈路を確保した後，ロクロニウム臭化物（6.0 mg）とアトロピン（0.05 mg）を静脈内投与した。次いで，セボフルレン吸入からプロポフォール（8.0 mg/kg/h）とレ



b

治療	P-ect+MCr		CRF	P-ect+CRJ	P-ect+CRJ	CRF		P-ect+MCr
齲蝕診断	C3	C0	C2	C3	C3	C2	C0	C3
歯式	D	C	B	A	A	B	C	D
歯式	D	C		A	A		C	D
齲蝕診断	C2	C0					C0	C3
治療	CRF							P-ect+MCr

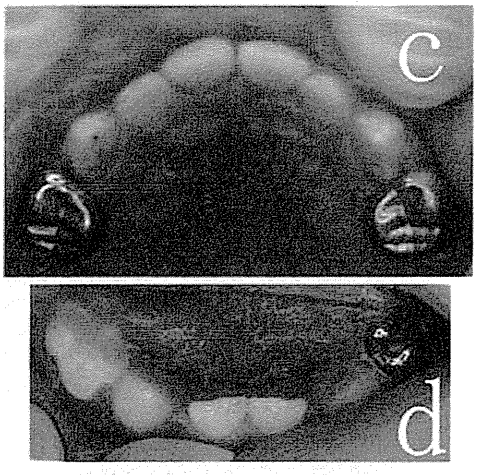


図4　GABRB3 全身麻酔下齲蝕治療時のデンタルエックス線写真，治療内容および治療後の口腔内写真（1 歳 7 か月時に施行）
a. 術中デンタルエックス線写真
b. 齲蝕診断および治療内容（CRF：コンポジットレジン修復，P-ect：抜髄・根管充填，CRJ：レジンジャケット冠装着，MCr：乳歯冠装着）
c. 治療後の上顎歯列（術中に撮影）
d. 治療後の下顎歯列（術中に撮影）

ミフェンタニル（0.3 μg/kg/min）の持続静脈内投与に切り替え，内径 4.5 mm の気管チューブを経鼻的に挿管した。挿管後は酸素投与下に，プロポフォール（9～12 mg/kg/h），レミフェンタニル（0.15 μg/kg/min）の持続静脈内投与により BIS 値 50～60 を目安に麻酔を維持した。歯科処置として，デンタルエックス線検査を行い齲蝕の重症度を診断した後，治療を行った（図 4 a～d）。治療終了後，自発呼吸，嚥下，開眼を確認し抜管した。手術時間は 2 時間 27 分，麻酔時間は 4 時間 41 分であった。術後は呼吸・循環動態ともに安定に経過し，治療翌日に退院した。退院後は当科を定期的に受診しており，現在のところ経過は良好である。今後も定期的な口腔衛生指導を継続する方針である。

考　察

AS は，重度精神遅滞，運動失調，てんかん，容易に誘発される笑いなど，主に中枢神経系の異常を特徴とする[2]。AS の原因遺伝子は *UBE3A* で，第 15 番染色体長腕 q11.2–q13 領域に存在する[3]。*UBE3A* はユビキチンを介したタンパク分解経路に関わる E3-ユビキチンリガーゼをコードする。ヒトの脳組織では，ゲノムインプリンティングにより母親由来の *UBE3A* のみ発現し，父親由来の *UBE3A* は不活化されている。一方，他の組織では両方の *UBE3A* に発現がみられる。したがって，何らかの要因で母親由来の *UBE3A* が機能喪失すると脳組織では *UBE3A* の発現が完全に消失することとなり，中枢神経系を中心に異常が出現すると考えられている[5]。しかし，その分子機序の詳細は解明されていない。

母親由来の *UBE3A* が機能喪失する要因として，母親由来第 15 番染色体長腕 q11.2–q13 領域の欠失が最も多く約 7 割を占め，本症例もこれに該当する[2]。この領域には *UBE3A* 以外にも多様な遺伝子が含まれているため，*UBE3A* 以外の遺伝子欠損に起因する多様な症状が出現する可能性がある[5]。GABA–A 受容体の β3 サブユニットをコードする *GABRB3* はその一つである[6]。*GABRB3* はゲノムインプリンティングを受けない[5]。しかし，*GABRB3* のヘテロ欠損により脳内の GABA-A 受容体機能に異常をきたし，てんかんの発症に関与すると考えられている[6]。したがって，今後は本症例においてもてんかん症状が出現する可能性が高い。本症例で観察された高振幅の不規則徐波は，AS の脳波所見の一型であり当院小児科で注意深く経過観察されている[7,8]。

AS の歯科口腔領域の特徴として，空隙歯列，下顎前突，薄い上口唇，厚い下口唇，摂食・嚥下障害，巨口，流涎をともなう舌突出などが報告されている[9,10]。特に，下顎前突，巨口，下口唇の肥厚は年齢が増すにつれて顕著となる。その他，下顎第二大臼歯の単根化や歯髄腔の拡大，乳歯エナメル質の低形成，永久歯列における正中離開が報告されている。本症例では，頭部・顔貌所見として尖ったオトガイおよび流涎による口角付近の皮膚発赤が認められた。口腔内所見として多数歯齲蝕および $\overline{\text{B}|\text{B}}$ の先天性歯牙欠損が認められた。現在のところ，これらの歯科口腔領域の症状の遺伝的背景については詳細不明である。本症例では母親由来第 15 番染色体長腕 q11.2–q13 領域が欠失していることから，この領域に含まれる何らかの遺伝子がこれらの症状に関与する可能性も考えられる。今後の研究課題として興味深い点といえる。

本症例では，多数歯齲蝕に対する対応として全身麻酔下での集中歯科治療を選択した。患児は AS の一徴候として重度の精神遅滞を合併していることに加えて，当科初診時は低年齢であった。そのため，デンタルエックス線検査および齲蝕治療のいずれに対しても，患児が協力を示すようになるまでにはかなりのトレーニングと時間を要することが予想された。齲蝕に対する診断と治療が遅れれば保存可能な歯数も減少し，後継永久歯歯胚および歯列咬合の健全な成長発育を阻害する危険も高くなる。口腔内に多数歯齲蝕として感染源を長期間放置することは，患児の全身の成長発育に対する阻害因子となり得る。以上の点を保護者に説明したところ，保護者の同意を得たため全身麻酔下にて集中歯科治療を施行した。

AS 患者に対する全身麻酔管理の注意点として，巨舌に伴う挿管困難，てんかん，筋緊張低下，迷走神経反射亢進などが挙げられる[11]。本症例では，挿管困難となりうる巨舌の所見はなかった。また，てんかんの発症も認めなかった。しかし，染色体検査結果から GABA-A 受容体の機能異常が強く示唆されるため，痙攣発作など麻酔薬に対する反応に注意を要すると考えられた[11–13]。そこで，痙攣誘発作用があるセボフルランは使用量を最小限に抑えるため麻酔導入時にのみ使用した。麻酔の維持は，プロポフォールとレミフェンタニルにて行った。筋弛緩薬は挿管前に臭化ロクロニウムを使用し術中の追加投与は行わなかった。術中，痙攣発作の予防のためミダゾラムを 1 mg ずつ 2 回投与した。迷走神経遮断のためアトロピン 0.05 mg を 1 回のみ投与した。以上の方法により，麻酔導入から術中，麻酔覚醒，抜管に至るまで呼吸および循環動態を安定に保つことができた。術後の経過も良好で，翌日に当院小児科を退院した。

本症例において齲蝕が多発した背景として，保護者への問診から，家庭での保護者による仕上げ磨きが不十分

であった点と，離乳食から普通食への移行に時間がかかり，卒乳が遅れていた点が挙げられる。いずれも重度の精神遅滞により患児の協力が得られにくいことが背景にあると考えられる。術後は齲蝕の再発と予防を目的とした一般的な口腔衛生指導は極めて重要となる。例えば，①フッ化物塗布・フィッシャーシーラントにより歯質を強化する，②十分な歯面清掃によりプラーク定着期間を減少させる，③夜間哺乳の習慣を徐々に改め規則正しい食習慣を確立する，④しょ糖類の摂取をコントロールしプラーク形成を抑制する，といった取り組みが挙げられる。また保護者の協力も不可欠である。齲蝕予防の重要性を保護者に十分に説明し，来院が中断しないよう当院小児科受診と合わせて定期的な口腔衛生指導を行っていく方針である。

結　論

我々は多数歯齲蝕を伴うASの1例を経験した。患児はASの中枢神経症状として重度の精神遅滞を合併し，かつ低年齢でもあったことから，全身麻酔下で集中歯科治療を施行した。術中および術後に合併症はなく，現在のところ経過は良好である。今後も，当院小児科と連携を取りながら定期的な口腔衛生指導を継続する方針である。

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Treatment of Severe Dental Caries in Patient with Angelman Syndrome : Case Report

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Angelman syndrome (AS) is a neurogenetic disorder characterized by severe mental retardation, ataxia, speech disorder, seizures, easily provoked laughter, and craniofacial anomalies. The cause of AS is loss of expression of the maternal copy of the UBE3A gene, which is located in the chromosome 15q11–q13 region and maternally expressed by genomic imprinting.

We encountered a 1-year-6 month-old boy with AS complicated by severe dental caries in many of his primary teeth. A diagnosis of AS had been established by specific clinical and genetic findings at the Department of Pediatrics of Kyushu University Hospital at the age of 1 year. The patient was referred to the Department of Pediatric Dentistry and Special Needs Dentistry at Kyushu University Hospital for diagnosis and treatment of dental caries. The patient was unable to cooperate for a dental examination in the outpatient clinic due to severe mental retardation associated with AS. To complete comprehensive dental assessments and treatment, intra-oral and dental X-ray examinations, as well as related treatments were performed under general anesthesia. The postoperative course was satisfactory and uncomplicated. Long-term follow-up is important in such cases for early diagnosis and management of the orofacial condition, because mandibular prognathism, enlarged tongue, widely spaced teeth, and enamel hypoplasia have been reported in AS patients.

Key words : Angelman syndrome, UBE3A gene, Genomic imprinting, Dental caries

鼻腔内の過剰歯を本院耳鼻咽喉科と連携し内視鏡下に摘出した1例

増田啓次[1)]　山座治義[2)]　西垣奏一郎[2)]
小笠原貴子[1)]　柳田憲一[1)]　廣藤雄太[2)]
野中和明[2)]

要旨：今回我々は，6歳8か月の男児の右鼻腔内に異所性過剰歯を認めた1例を経験した。患児の初発症状は鼻出血と鼻汁で抗菌薬投与でも改善しなかった。かかりつけの耳鼻科にて行われた鼻腔の内視鏡検査により，異所性歯の存在が疑われ当科を紹介された。当科にて単純CT検査を施行したところ，右鼻腔底前方に過剰歯を認めた。過剰歯の形態は犬歯様で，歯根相当部は軟組織腫瘤に包まれ鼻腔内に孤立して存在していた。上顎骨の吸収像および乳切歯・永久切歯歯胚の位置異常は認めなかった。本院耳鼻咽喉科と連携し，鼻内より内視鏡下に過剰歯を含む有茎性の腫瘤を切歯孔へと続く基部で切除し腫瘤と過剰歯を一塊として摘出した。摘出物の病理組織所見では，過剰歯はエナメル質，象牙質，セメント質が正常な歯と同様に配置された構造をしていた。しかし，歯髄は壊死し歯の周囲には炎症性肉芽組織の増生を認め，本過剰歯が難治性の鼻症状の原因と考えられた。現在のところ術後の経過は良好である。再発に注意しながら経過観察を行う方針である。

Key words：鼻内歯，正中歯，内視鏡手術

緒　言

小児歯科臨床において，鼻腔内に異所性に萌出した過剰歯に遭遇することはまれである。鼻腔内に萌出した過剰歯の多くは，萌出位置が鼻腔底の前方付近であることから，上顎骨正中部内に発生する過剰歯（以下，正中歯）との関連が示唆される[1–3]。歯科領域で一般に普及している撮影法のうち，鼻腔が撮影範囲に含まれるパノラマエックス線写真では上顎前歯部の鼻腔底付近が描出されにくい。低年齢の小児では，撮影に協力が得られず体動によりさらに画像が不鮮明になりやすい。また，鼻鏡や内視鏡による鼻腔内の診察は歯科領域では通常行わない。したがって，一般の小児歯科臨床においては明らかな鼻症状があった場合でも，鼻腔内の過剰歯を発見し診断することは容易ではない。

今回我々は，6歳8か月の男児の右鼻腔底に異所性に萌出した過剰歯の1例を経験した。本院耳鼻咽喉科と連携して治療を行ったので考察を加え報告する。なお，本症例の公表について保護者の同意を得ている。

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（2014年5月7日受付）
（2014年8月1日受理）

症　例

患児：初診時年齢6歳8か月（男児）
主訴：鼻腔内異物の精査・加療
現病歴：当科を受診する約1か月前より鼻出血と鼻汁が出現し，しだいに増悪したためかかりつけの耳鼻科を受診した。慢性副鼻腔炎と診断され抗菌薬投与を受け経過観察されていた。しかし，鼻症状が改善しないため鼻内視鏡検査を受けたところ，右鼻腔内に歯に類似する異物を認めた。同異物の精査・加療を目的に当科を紹介された。
既往歴：喘息
1歳頃に発症し，2歳時に最終発作を認めた後，投薬治療にて喘息症状はしだいに改善した。当科初診時には使用中の喘息治療薬はなかった。
家族歴：特記事項なし
身体所見：身長110.9 cm，体重21.3 kg（ローレル指数156）で，食欲不振なく顔色は良好であった。顔貌は左右ほぼ対称で，鼻部の腫脹・発赤・自発痛は認めなかった（図1a，b）。鼻腔内の異物は鼻孔からの視診では確

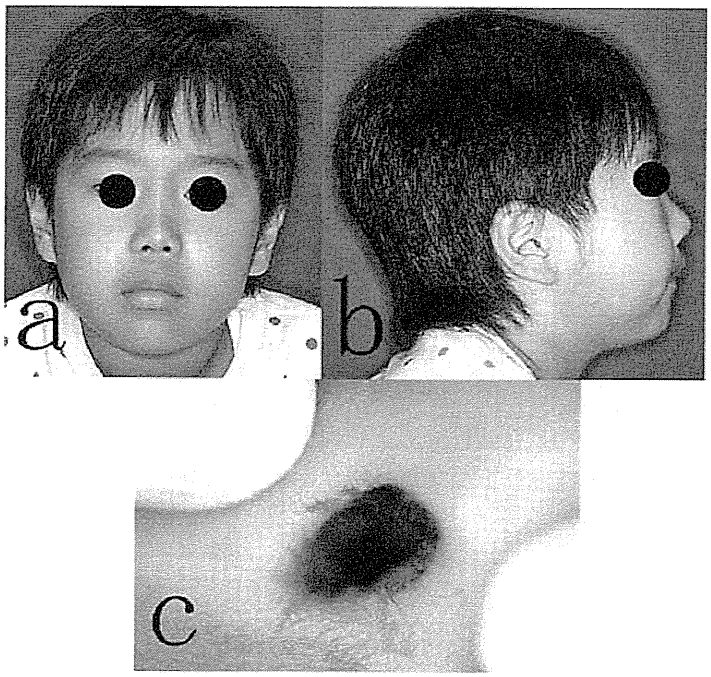

図1　顔面写真
a. 正貌　　b. 側貌　　c. 右鼻孔拡大

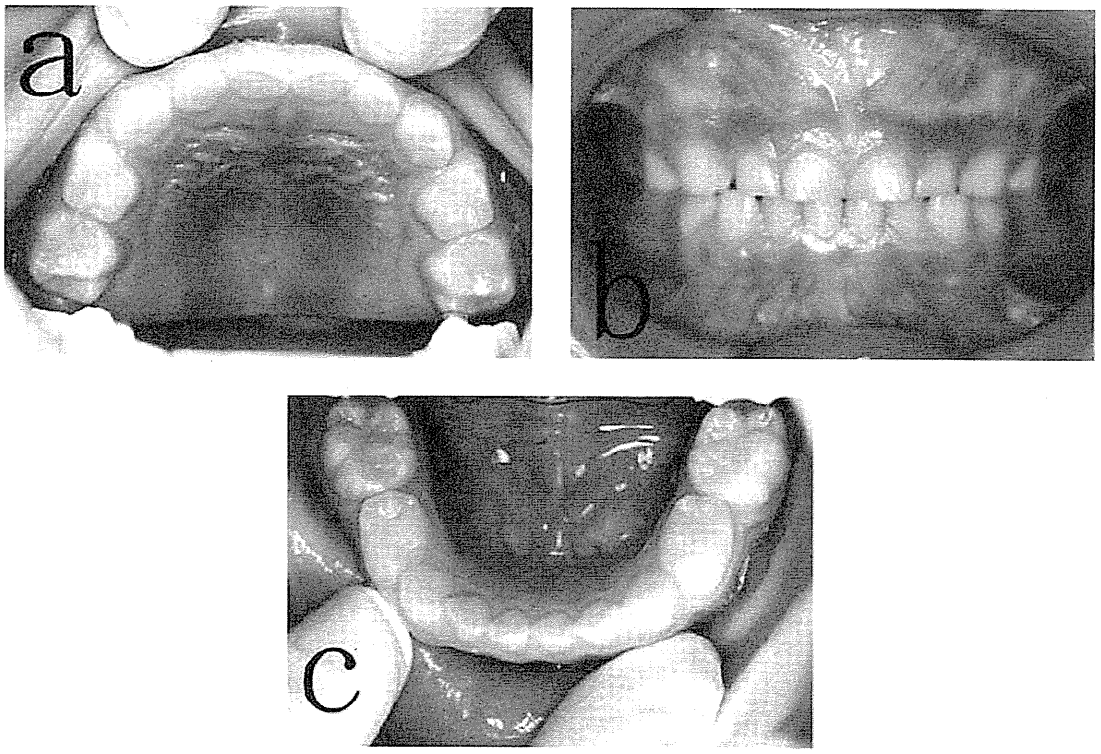

図2　口腔内写真
a. 上顎歯列　　b. 正面　　c. 下顎歯列

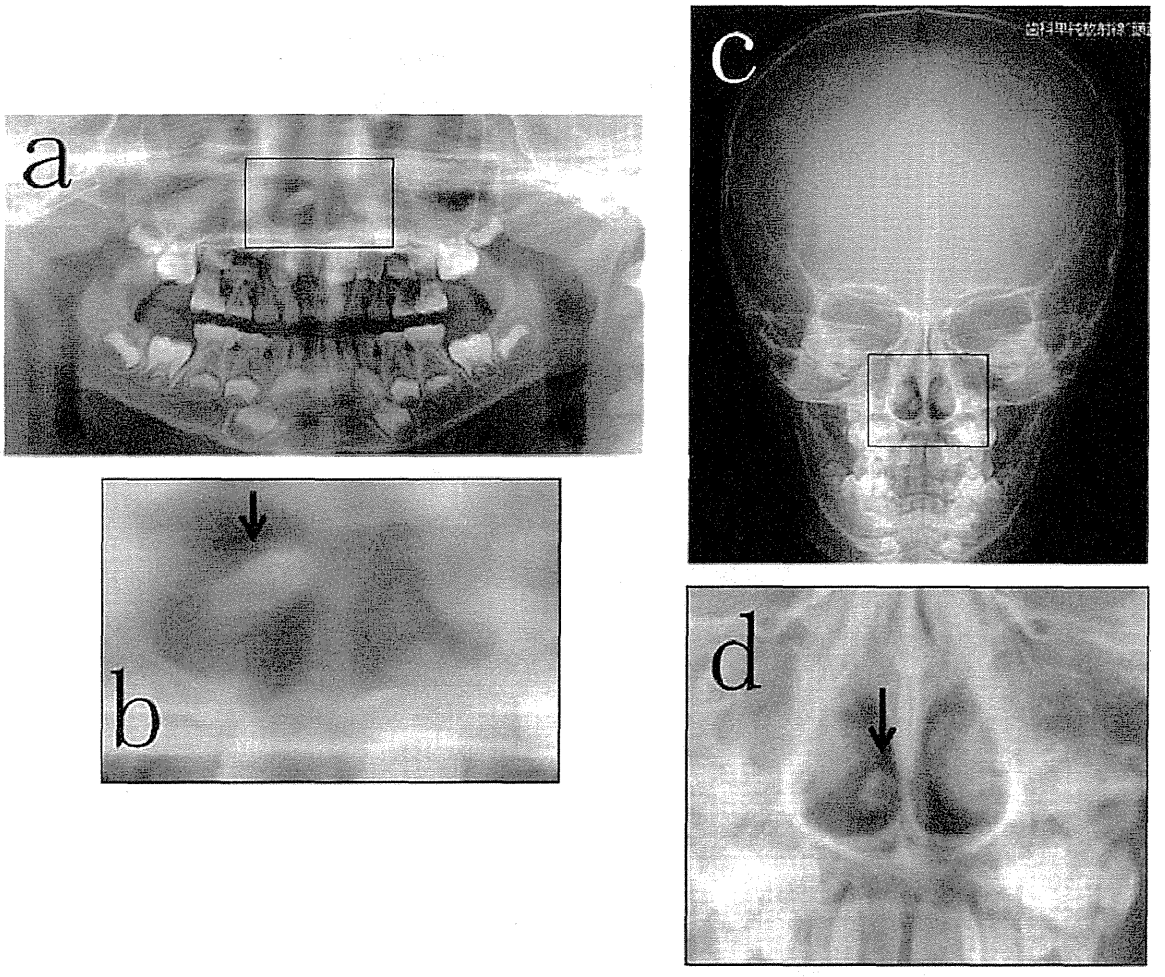

図3　パノラマエックス線写真および頭部単純エックス線写真
a. パノラマエックス線写真
b. a の四角内の拡大図（矢印：歯様構造物とみられる不透過像）
c. 頭部単純エックス線写真
d. c の四角内の拡大図（矢印：歯様構造物とみられる不透過像）

認はできなかった（図 1 c）。口腔内所見として，歯肉および口腔粘膜に特記すべき異常所見は認めなかった。歯の所見として Hellman の歯年齢ⅡA 期で，視診・触診では歯数の異常，歯列不正，歯の実質欠損および形成不全は認めなかった（図 2 a～c）。

画像所見：パノラマエックス線写真および頭部単純エックス線写真にて右鼻腔内に，やや不鮮明なエックス線不透過像を認めた（図 3 a～d）。上下顎とも顎骨内に異常な透過像および不透過像は認めなかった。永久歯歯胚数の異常は認めなかった。CT 検査では，右下鼻道の前方やや正中寄りに紡錘形の歯に類似するエックス線不透過物を認めた（図 4 a～d）。その長軸はほぼ水平で前後方向を向いていた。中心部には長軸に沿って歯髄腔様の管腔構造を認めた。前方部は歯冠に，後方部は歯根にそれぞれ類似していた。後方部の約 2/3 は，周囲を軟組織に包まれ鼻腔底粘膜に連続していた（図 4 c）。1 歯胚は上顎骨内に存在し明らかな位置異常は認めなかった（図 4 b）。1 歯胚と同異物との連続性も認めなかった。

臨床診断：右鼻腔内の過剰歯

処置および経過：患児の鼻症状は，右鼻腔内の過剰歯に起因するものと考えられた。また，画像所見から過剰歯は右鼻腔内に完全に孤立して存在していると考えられた。そこで，当院耳鼻咽喉科と連携し，なるべく早期に全身麻酔下にて鼻内から内視鏡下に同過剰歯を摘出する方針とした。

術中，鼻腔内を観察すると鼻腔入口部付近の総鼻道底