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Case Report

A Case of Nager Syndrome Diagnosed Before Birth

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Nager syndrome is a rare disease involving severe micrognathia and upper limb shortening. In this report, we describe a case in which micrognathia of the fetus was suspected based on the observation of upper limb shortening during detailed B mode and 3D/4D ultrasonographic observation, and combined fetal MRI and 3D-CT led to a prenatal diagnosis of Nager syndrome. Upon birth, because severe micrognathia caused airway obstruction and made it difficult to spread the larynx for intubation, effective ventilation could not be carried out and a tracheostomy was necessary. Since a differential diagnosis of Nager syndrome can be made based on the fact that micrognathia typically co-occurs with upper limb shortening, it is possible to diagnose the disease before birth and prepare for life-saving measures accordingly.

Key words: Nager syndrome, acrofacial dysostosis, micrognathia, jaw index, SF3B4

Nager syndrome, also known as *Acrofacial Dysostosis 1, Nager type*, is a disease involving severe micrognathia and upper limb shortening, and was first reported by Nager and Reynier in 1948 [1]. In a 30-week-old fetus with polyhydramnios, Nager syndrome can be diagnosed before birth by ultrasound findings of significant mandibular hypoplasia, auricular malformation, and poor osteogenesis of the long bones of the arm [2-5]. There have been very few reports of Nager syndrome in Japan; furthermore, we could only find one case report on diagnosis before birth [6], with no published reports on the implementation of MRI or CT photography during the fetal period in any of the literature. In this study, we used B mode and 3D/4D ultrasonography for detailed observation of the fetus, together with fetal MRI and 3D-CT, and delivered the child well prepared for the likelihood of Nager syndrome.

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Case Report

The mother was a 27-year-old woman primigravida. There was nothing of note in her family or personal medical history. At the 26th week of a natural pregnancy, her doctor had discovered polyhydramnios, bone defects in both forearms, and a ventricular septal defect. Due to polyhydramnios, esophageal closure was suspected. An amniotic diagnosis (G-banding method) revealed 46, XY. She was introduced to our hospital for further examination and management at the 32nd week of pregnancy. On fetal ultrasonography at the 34th week of pregnancy, the estimated body weight was 2,056 g (-0.8 SD). We also checked the fetal stomach cells and found severe polyhydramnios at an amniotic fluid index (AFI) of 54 cm. Using sagittal-section imaging on the fetal face, we observed a remarkable decline in the formation of the chin and diagnosed microg-

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nathia due to the interior facial angle (IFA) being set at 30 degrees (Fig. 1). In addition, fetal facial findings using a 4D probe revealed micrognathia with the rima palpebrarum tilted diagonally downward (Fig. 2). The length of the upper limbs was 7.4 cm from shoulder to fingertip. The antebrachial bone and humerus were fused together, making it difficult to visualize and indicating significant upper limb shortening. Only four fingers could be confirmed (Fig. 3). No abnormal findings were found in the lower limbs. Fetal MRI also revealed shortening of the upper limbs and micrognathia (Fig. 4). Upon a fetal 3D-CT examination at 36 weeks and 0 day of pregnancy, mandibular hypoplasia and fusion of the humerus, radius and ulna were observed, along with a thumb fracture (Fig. 5). From the above findings, Nager syndrome was suspected. Taking ex-utero intrapartum treatment (EXIT) into consideration, the mother was found to have suffered a

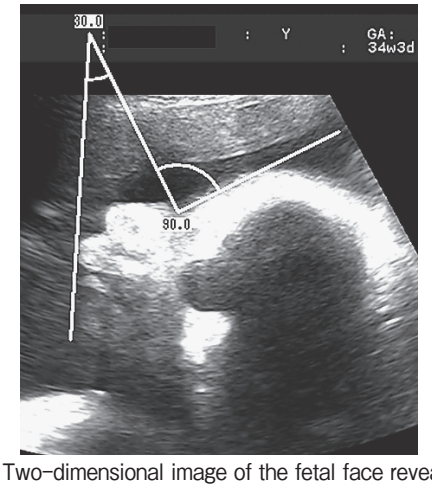

Fig. 1 Two-dimensional image of the fetal face reveals a small lower jaw.

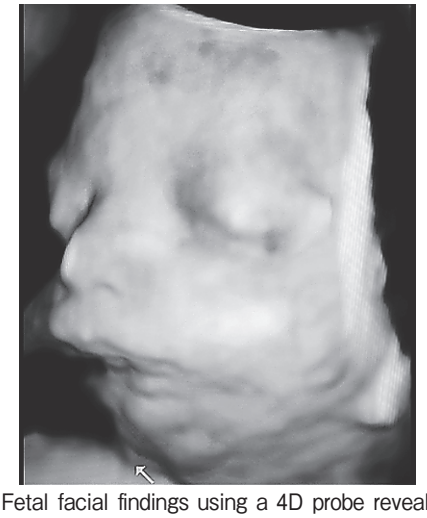

Fig. 2 Fetal facial findings using a 4D probe revealed micrognathia with the rima palpebrarum diagonally downward.

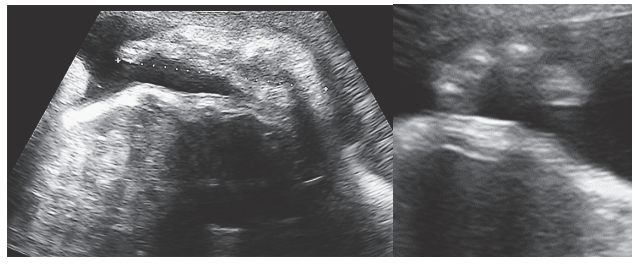

Fig. 3 Remarkable shortening of the upper limbs was observed, with only 4 fingers visible on both hands.

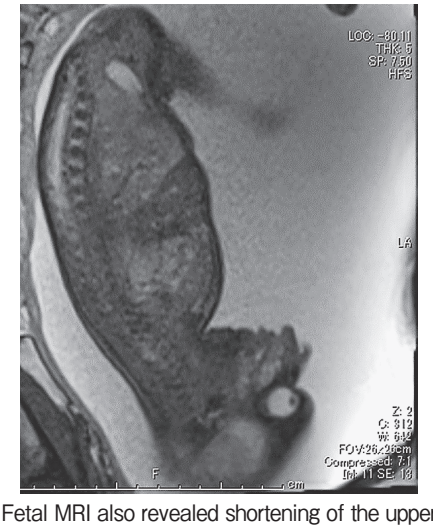

Fig. 4 Fetal MRI also revealed shortening of the upper limbs and micrognathia.

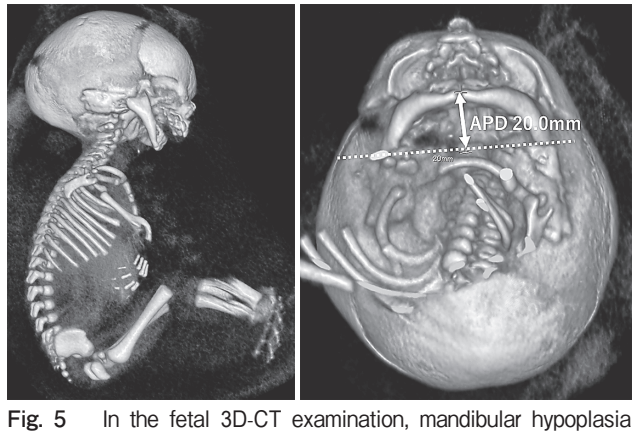

Fig. 5 In the fetal 3D-CT examination, mandibular hypoplasia and fusion of the humerus, radius and ulna were observed, along with a thumb fracture.

premature rupture at 36 weeks and four days of pregnancy and was therefore hospitalized. With a gradual change to real labor contractions at 36 weeks and six days of pregnancy, a 2,033 g boy was delivered through the vagina with an Apgar score of 2 points (1 min) / 5 points (5 min). The umbilical arterial blood gas analysis was pH 7.284. At birth, there was no initial crying and no muscle tonus. Although the boy was immediately moved to the resuscitation bed by a neonatologist and bag ventilation was carried out, we observed systemic cyanosis with a bradycardia of 70 beats/min. Insertion of a laryngeal mask did not provide effective ventilation. Although endotracheal intubation was attempted, we could not spread the larynx due to significant micrognathia and glossoptosis. Only with a bag mask could ventilation be carried out. Two min after birth, the baby's heart rate was constant above 100 bpm. However, 5 min after birth, the SpO2 decreased to 80% and systemic cyanosis and muscle tonus reduction continued. We determined that it was necessary to establish a surgical airway and so had a waiting pediatric surgeon perform a tracheostomy 17 min after birth. With a tracheotomy tube (Shiley 3.0NEO) inserted, an airway was established 37 minutes after birth. Related findings included a ventricular septal defect, bilateral radius defect, bilateral fibular defect, clubfoot, auricular low position, closure of both ear canals, syndactylism, diagonally downward rima palpebrarum and micrognathia (Fig. 6, 7). The significant polyhydramnios observed at the fetal stage was thought to be a result of dysphagia from the micrognathia-related glossoptosis. Genetic analysis was approved by the Ethical Committee of Okayama University Hospital; findings of c. 1060dupC, p.Arg354Pro fs*132 suggested a splicing factor 3b, subunit 4 (SF3B4) genetic mutation, resulting in a definitive diagnosis of Nager syndrome. As the genetic material in question was categorized as *de novo* in a previous report, genetic testing was not conducted on the parents. The baby is currently 2 years old. With a heart septal defect hole of 2 mm, he is under observation by the Department of Pediatric Cardiology. His external auditory canal is closed with no abnormalities in the inner ear structure. In an ABR examination, both ears had no response until -80 db, so the use of a bone conduction hearing aid was initiated from the eighth month after birth. For clubfoot, a cast was applied one month after birth and an Achilles tendon tenotomy was carried out by an orthopedist at the fourth month after birth, at which time the cast was changed to a Denis-Browne apparatus. For brachygnathia and lockjaw, deglutition training was performed along with tubal feeding during oral surgery. Opening of the mouth may be limited to approximately 1 cm at adolescence, necessitating elongation surgery in the future. Regarding motion restrictions due to a fibular defect, motion training and home-visit rehabilitation are being carried out. As for the motor development process, he was able to change positions at age one, sit up at age 1 year and 4

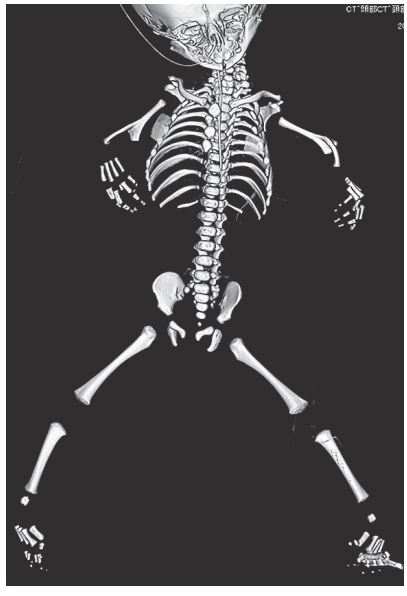

Fig. 6 Day 1. Upon CT, bilateral radial defects, fusion of the shortened ulna and humerus, and bilateral fibula defects were observed.

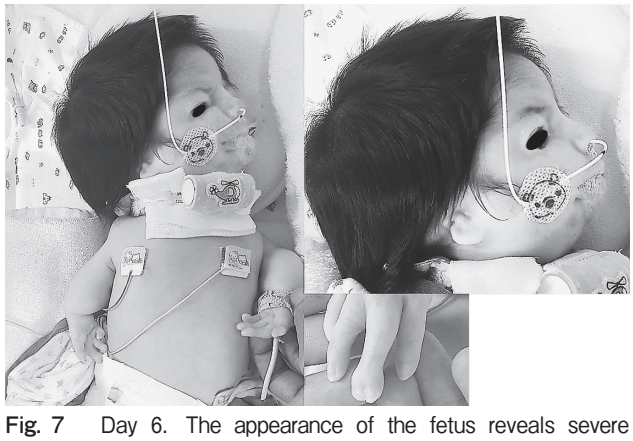

Fig. 7 Day 6. The appearance of the fetus reveals severe micrognathia, auricular low position, syndactylism and upper limb shortening.

months, and rise to standing at age 1 year and 9 months. Gastrostomy will be carried out at age 2 years and 1 month.

Discussion

We experienced a case of Nager syndrome that we could diagnose before birth. This case provided 2 clinical implications. When ultrasonography reveals upper limb shortening and polyhydramnios, it is vital to check for the occurrence of micrognathia in the fetal face. If found, a differential diagnosis of Nager syndrome is made. The other implication is that, in cases such as this, the degree of the disorder must be objectively evaluated, the blockage of the upper wind pipe removed, and a strategy (including EXIT) to keep it open discussed.

In Nager syndrome, polyhydramnios due to micrognathia-induced glossoptosis is often observed. Since the incidence of Nager syndrome is very rare, we often assume Pierre Robin syndrome or Treacher-Collins syndrome based on micrognathia alone. Since there is no occurrence of upper limb shortening in the above 2 syndromes, an examination of the upper limbs is extremely useful for differential diagnosis. However, the differential diagnosis also includes Miller syndrome, which also combines micrognathia and upper extremity deformities. Nager syndrome necessarily involves defects of the little digits of the upper/lower extremities, with this case characterized by a first finger defect of the upper extremities. Therefore, a differential diagnosis of Nager syndrome can be done by 3D-CT. Furthermore, the fact that Miller syndrome is associated with a cleft lip and palate may be a distinguishing factor [7]. Fetal factors associated with polyhydramnios may include fetus dysphagia, congenital muscle disease, chromosomal abnormalities, and fetal polyuria as distinguishing factors. If upper limb shortening and micrognathia can be found by fetus ultrasound, a prenatal diagnosis of Nager syndrome can be made.

As previously mentioned, for similar cases in which a micrognathia is found, it is necessary to remove the blockage of the upper wind pipe after delivery and discuss a strategy (including EXIT) to permanently reopen it immediately after the child is born. EXIT is a procedure carried out during caesarean sections, wherein the fetus is partial delivery and treatment are carried out simultaneously, via an incision in the uterus while maintaining the fetal placental circulation. Generally, if upper airway narrowing occurs immediately after delivery due to giant neck tumors or congenital laryngeal closure and it is presumed difficult to establish the airway after delivery, it is subject to debate whether tracheotomy should be performed immediately after birth or the fetus should be delivered using EXIT under placental circulation. Micrognathia causes upper airway obstruction. It is not an absolute indication for EXIT, and may cause complications in mothers such as increased bleeding. In order to judge the adaptation of EXIT, it is proposed to evaluate the mandible using the IFA or jaw index. The IFA is calculated by measuring the angle made by the cross section of a line orthogonal to the forehead at the level of the nasofrontal suture and a line from the tip of the mentum to the anterior border of the more protrusive lip on a sagittal view. The average IFA is 65.5 ± 8.1°, and windpipe clearance must be considered when the IFA is less than 50° [8]. The jaw index depicts the mandibular bone in B mode and is calculated by anterior-posterior diameter (APD)/biparietal diameter (BPD) × 100 [9]. The average jaw index is 40.0. The 5th percentile is 33.5. This case confirms that while there are difficulties involved in the depiction of the lower jaw via B mode due to the position of the fetus, fetal MRI can be used to assess the jaw index, as in previous cases [10].

In the present case, since it was possible for the mandibular bone of the fetus to be drawn by 3D-CT, we were able to make a visual assessment at the rear of the jaw. This generated scores of 20 mm for APD and BPD results of 90.22 mm when an ultrasound was conducted at the time 3D-CT images were taken (Fig. 5). These values indicated a clear case of micrognathia. As respiratory management of Nager syndrome, some studies have reported cases in which an airway could provide good ventilation against intubation difficulty [11]. In this case, although we could not spread the larynx for endotracheal intubation due to micrognathia, ventilation could be carried out using a bag mask. Furthermore, if one were to take into account cases where the life of the fetus was saved although a diagnosis was not made until the time of birth, Nager syndrome might be considered a syndrome that is stabilized by the application of prompt respiratory care, such as windpipe incisions, and one that does not require the application of EXIT [12-13]. However, it is still far preferable to use both IFA and a jaw index to objec-

tively evaluate the disorder and to prepare for any upper windpipe blockages immediately after birth than to enter such a situation "blind". This case was in the range of asphyxia of newborns with an Apgar score of five points for the five-minute interval value. It cannot be ruled out that asphyxia at birth had some influence. Going forward, it will be necessary to evaluate the applicability of EXIT more carefully via the accumulation of similar cases.

Nager syndrome has been variously reported to occur sporadically, without a clear pattern, and to run in families, suggesting autosomal dominance or autosomal recessiveness [14-15]. Recent genetic analyses have identified a mutation of the SF3B4 gene as the cause of disease [16-18]. Although the intelligence of those with Nager syndrome is said to be normal, the disease may be accompanied by hearing impairment, which may cause delayed speech [19]. Upper limb shortening varies from a mild condition involving only hypoplasia of the first finger to conditions exhibiting humerus and forearm bone defects. There have been no reports on lower extremity abnormalities as of yet. In this case, it is worth noting that there was a defect in both fibulas. The rate of newborn stillbirths and deaths is said to be 20% [20].

Fetal micrognathia is highly associated with malformation complications including fetal development failure, bone heteroplasia, congenital heart disease, and polyhydramnios. The diagnosis of micrognathia alone is very rare. In this case, we used the fact that remarkable shortening of the upper limbs accompanies micrognathia in Nager syndrome to develop our prenatal diagnosis and cooperate with other departments prior to birth, so that a timely tracheostomy for airway obstruction could be performed immediately after birth.

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