Partial deletion of the long arm of chromosome 11: ten Japanese children


The clinical features of partial deletion 11q were correlated with the size of the deleted region. Ten Japanese children with partial deletion of 11q were investigated. They were divided into three groups. Three patients in the first group had interstitial deletions and preserved subband q24.1. Six patients in the second group demonstrated terminal deletion of 11q including subband q24.1, with typical features of 11q− syndrome (Jacobsen syndrome). The third group included only one patient, who had terminal deletion of 11q without characteristics of typical 11q− syndrome. Prominent features of patients in the first group included severe mental and motor developmental delay, seizures, cleft lip and palate, and ophthalmological findings. Patients in the second group showed mild to moderate developmental delays without deterioration. Abnormalities in neuroimages, high intensity in the cerebral white matter in T2-weighted magnetic resonance (MR) images, and recurrent infections were not observed after the age of 7 years. The subject in the third group, with the smallest amount of deleted chromosome, did not show developmental delays, suggesting that some unknown genes related to developmental delays may be located adjacent to subband q24.1. Variation in the deleted parts of 11q resulted in different clinical features in each group.

Key words: chromosome abnormality – chromosome 11 – Jacobsen syndrome – long arm – partial deletion

Jiro Ono1,*, Tomoko Hasegawa2, Seiichi Sugama3, Nobuyuki Sagehashi4, Yutaka Hase5, Kikuko Oku6, Yoko Endo7, Shozo Ohdo8, Satoshi Ishikiriya9, Hiroko Tsukamoto1 and Shintaro Okada1

1Department of Pediatrics, Faculty of Medicine, Osaka University, Osaka, 2Division of Clinical Genetics and Cyrogeneitcs, Shizuoka Children’s Hospital, Shizuoka, 3Department of Pediatrics, Tokyo Jikei University School of Medicine, Tokyo, 4Department of Plastic Surgery, Maebashi Red Cross Hospital, Gunma, 5Shiroma Public Health Center of Osaka City, Osaka, 6Division of Neonatal Intensive Care, Kawaguchi Municipal Medical Center, Tokyo, 7Department of Pediatrics, Shinshu University School of Medicine, Nagano, 8Division of Pediatrics, National Sanatorium Miyazaki Hospital, Miyazaki, 9Division of Medical Genetics, Chiba Children’s Hospital, Chiba and 10Division of Pediatrics, Toyonaka Municipal Hospital, Osaka, Japan

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Over 40 patients with terminal deletion of 11q, also known as Jacobsen syndrome, have been reported since the first case was described by Jacobsen et al. (Jacobsen et al. 1973, Faust et al. 1974, Turleau et al. 1975). Of the patients who have been described, approximately a quarter have died during the first year of life primarily because of a tendency to bleed, infection, and/or congenital heart defects (Schinzel et al. 1977, Léonard et al. 1979, McPherson and Meissner 1982, Helmuth et al. 1989). However, patients who have survived this period show fairly good life prognosis. Although the most frequent chromosomal break point in the patients was 11q23, there were also patients whose break points were q21 (Faust et al. 1974, Helmuth et al. 1989), q22 (Linarelli et al. 1975, Felding et al. 1979) or q24 (O’Hare et al. 1984, Fryns et al. 1986, Schwarz et al. 1992). It is generally accepted that the deletion of subband q24.1 plays an important role in the expression of the typical manifestations of 11q−, e.g., trigonocephaly, frontal bossing, ptosis, hypertelorism, epicanthal fold, flat

In the present study, we examined the relationship between deleted bands of 11q and clinical features in ten Japanese patients who possess partial deletion of 11q, including three patients with interstitial deletions of 11q. Growth charts and the mental and motor development of six typical 11q− patients were also investigated.

Subjects and methods

Ten Japanese children, four boys and six girls, who possess partial deletion of 11q were included in this study. They ranged between 3 and 13 years of age at investigation. We investigated the following features: deleted portion of the chromosome (seven of ten were high resolution analysis), condition at birth, physical growth, motor and mental development, accompanying symptoms and anomalies, blood tests, and neuroimaging if available.

The ten patients were divided into three groups. The first group included patients with interstitial deletion of 11q, and the second group included six patients with terminal deletion (q23–qter), or “11q− syndrome (Jacobsen syndrome)”. The third group included only one patient, who had terminal deletion (q24–qter). This patient presented with the least deletion in this cohort of patients.

Results

Our results have been summarized in Fig. 1. The gestational age was between 38 and 42 weeks in eight patients. Obvious intrauterine growth retardation (IUGR) was observed in three patients (patients 4 and 8), both of whom belonged to the second group. All patients but one demonstrated retarded physical growth below the mean, and four were less than −2SD. All but one patient (patient 10) revealed delayed motor and mental development.

Group 1. All patients in this group had retinal dysgenesis, seizures, and delayed motor and mental development. Patients 1 and 3 showed severe motor and mental developmental delay, though they did not experience any significant medical problems, such as intracranial hemorrhage, during their neonatal periods. Cleft palate was observed in two patients. Patient 3, whose interstitial deletion extended to q23.3, showed some features characteristic of typical 11q− syndrome, i.e. hypertelorism, thin upper lip, high-arched palate, micrognathia, short neck, and recurrent infection. However, he did not have a congenital heart defect.

Group 2. Motor and mental developmental delay and thin lips were observed in all patients in this group.

These patients had better motor than mental development and all were able to run during their childhood. Frontal bossing, epicanthal folds, low-set ears, high-arched palate, and congenital heart defects were found in five patients. Four patients had ptosis, flat nasal bridges, upturned noses, short necks, and accessory nipples. These symptoms seem to comprise the core of 11q− syndrome. All six patients developed physically at a level much lower than the mean. Two subjects (patients 6 and 9) had body heights of less than −2SD at the first examination and throughout the follow-up period. Patients 4 and 8, who showed IUGR, did not suffer from dwarfism.

Group 3. Only one patient (patient 10) is included in this group. She presented with deformity of the fingers, a congenital heart defect, failure to thrive, and recurrent infections. This is the only patient in this study who did not show significant motor and mental developmental delays.

Cranial MR imaging was performed on four patients in the second group. Two patients who were older than 7 years of age showed no abnormal myelination, though one of them showed dilatation of the lateral ventricles. On the other hand, two patients on whom MR imaging was performed before the age of 3 years demonstrated abnormally high intensity areas in the white matter in T2-weighted images.

Laboratory examinations were performed on seven patients during childhood. Only one patient (patient 5) presented thrombocytopenia (79×10⁹/mm³), which is a characteristic manifestation of this syndrome during the neonatal period. The other patients presented with platelet counts of more than 100×10⁹/mm³.

Discussion

According to reports, a quarter of all patients with terminal deletion of the long arm of chromosome 11 have died during the neonatal and infantile periods (Schnizel et al. 1977, Léonard et al. 1979, McPherson and Meissner 1982, Helmuth et al. 1989). Major factors that determine the prognosis of patients with this syndrome include accompanying cardiac anomalies, tendency to bleed, and recurrent severe infections. The patients reported in this paper survived beyond the neonatal and infantile periods.

There is controversy over which band is respon-
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<tr>
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<td>8 years</td>
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![Gestation, Birth weight, and other features](chart)

**Fig. 1.** List of 11q- patients included in this study. Vertical black bars show the range of deletion of the long arm of chromosome 11. Plus (+), minus (−) and plus/minus ± indicate positive, negative and probable, respectively.

Sensible for the expression of the typical manifestations of 11q- syndrome (Jacobsen syndrome). O'Hare et al. reported that an 11q- patient who had deletion of q24.1-qter presented typical features of 11q- syndrome, and Fryns described an 11q- patient with deletion of q24.2-qter who showed an absence of typical manifestations (O'Hare et al. 1984, Fryns et al. 1986). It follows that subband q24.1 may be considered critical in the expression of the characteristic symptoms of 11q- syndrome. Endo et al. (1993), in a literature review of research on patients with 11q- syndrome with (31 patients) or without (7 patients) deletion of subband 11q24.1, also argues that subband 11q24.1 is responsible for the expression of the characteristic manifestations of this syndrome. The findings of these studies coincide with the fact that patient 10, who presented with deletion of q24.2-qter on chromosome 11, lacks typical clinical features of 11q- syndrome. This is the only patient in this study who did not show mental or motor developmental delays. This implies that one of the genes related to mental and motor developmental delay may be located in this area.

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The patients with interstitial deletion of 11q that did not include subband q24.1 showed either less pronounced or no signs of 11q—syndrome and demonstrated other abnormal features such as cleft palate and lip, iris coloboma and high-arched palate (McPherson & Meissner 1982, Tailleimite et al. 1975, Bateman et al. 1984, Klep-De Pater et al. 1985, Guć-Śęcki et al. 1989). Group 1 in the present study demonstrated clearly different manifestations from patients in the second group, who had deletion of q23-qter. However, patient 3 demonstrated some of the typical features of 11q—syndrome, suggesting that some overlap may exist between Groups 1 and 2.

Six patients with symptoms typical of 11q—syndrome were investigated. All showed Developmental Questionnaire Scores between 40 and 60. None of the patients showed deterioration, suggesting that this disorder is not degenerative. Only two patients (6 and 9) out of six in Group 2 seemed to experience dwarfism (less than −2SD). These patients did not have growth hormone deficiencies. In most patients, the growth data obtained at the first examination during the infantile period or early childhood gave a close approximation of the child's future growth. Although a similar portion of the chromosome was deleted in all patients in Group 2, clinical manifestations differed from patient to patient. More detailed analysis of the deleted parts of the chromosome is necessary in future studies.

cranial MR imaging performed before the age of 3 years demonstrated abnormally high intensity in the white matter, considered to be delayed myelination, demyelination or gliosis. In patient 8, serial MR imaging, performed at 1-year intervals, revealed that the abnormally high intensity areas could be considered to be delayed myelination, since the extent of abnormal intensity decreased with age (Ono et al. 1994). Normal myelination, which was confirmed by MR examination of the older patients, also supported our delayed myelination hypothesis. Wardinsky et al. reported similar MR findings in their studies of 11q—syndrome (Wardinsky et al. 1990).

Recent progress in gene analysis has demonstrated that the gene for the neural cell adhesion molecule (NCAM) is located on band 11q23 (Nguyen et al. 1986, Berube et al. 1990). It is speculated that a reduced amount of gene encoding NCAM in 11q deletion patients causes delayed myelination (Ono et al. 1994). The majority of patients with terminal deletion of 11q suffer from recurrent infections as infants or during early childhood. Low levels of CD56, the surface marker of the natural killer cell (NK), may be related to the fact that CD56 is identical to NCAM (Lanier et al. 1989, Husmann et al. 1989). As with the late childhood disappearance of developmental delays in myelination, in late childhood, NK cells may regain their functions, leading to the elimination of recurrent infections.

References


Ono et al.


