18p— SYNDROME ASSOCIATED WITH HEMIVERTEBRAE, FUSED RIBS AND MICROPENIS¹

Shozo NAKANO,* Takehiko OKUNO,** Hiroatsu HOJO,**
Shinichi MISAWA,*** and Tatsuo ABE***

*Department of Pediatrics, Kansai Denryoku Hospital, Osaka, Japan

**Department of Pediatrics, Kyoto University school of Medicine, Kyoto, Japan

***Department of Medicine and Preventive Medicine, Kyoto Prefectural University of
Medicine, Kyoto, Japan

Summary An 11-month-old boy was found to have deletion of the short arm of chromosome 18. He was a short hypotonic infant with thoracic hemivertebrae, fused ribs and micropenis in addition to developmental delay, ptosis of the eyelids, epicanthal folds, hypertelorism, large prominent and low-set ears, micrognathia and short neck.

Banding analysis showed the patient's karyotype to be 46, XY, *del*(18)(p1103).

INTRODUCTION

Since their first report in 1963, de Grouchy *et al.* (1963, 1969) have summarized 23 cases with deletion of the short arm of chromosome 18. They noted the variability of the clinical features of the 18p— syndrome. More than 80 cases have been listed in the literature, and the deletion syndrome seems to represent a combination of clearly defined malformations (Faust *et al.*, 1976).

The case reported here is a boy who had a chromosome constitution of 46,XY, *del*(18)(p1103). He showed in addition to major clinical signs, hemivertebrae, fused ribs and micropenis, which had not previously been reported in this syndrome.

CASE REPORT

The propositus, an 11-month-old boy, was the only child of a 32-year-old mother and a 38-year-old father. There was neither family history of malformations nor consanguineous marriage. His mother had no history of abortions. The pregnancy was complicated by severe abdominal pain and upper respiratory infection in the third month of pregnancy.

The patient was born after 42 weeks of gestation, weighed 2,060 g at birth. He complained of failure to thrive and retarded development, not controlling his head until 9 months of age. Physical examination revealed a short hypotonic infant.

Received February 10, 1977

¹ Supported in part by a grant from the Ministry of Health and Welfare, Japan.

Fig. 1. Patient at 10 months of age. Note ptosis, epicanthal folds, hypertelorism, large prominent and low-set ears, downturning corners of the mouth, micrognathia, short neck with left torticollis and right hemihypertrophy.

Fig. 2. Anterior-posterior view of thorax. Arrows indicate thoracic hemivertebrae and fused ribs.

At 7 months of age, his weight (6.4 kg) and height (63.6 cm) were below the 3rd percentile and the head circumference (42.8 cm) was in the 10th percentile for his age. At the chronological age of 54 weeks, motor development was that of 36 weeks, adaptive that of 40 weeks and social that of 35 weeks. His overall developmental

quotient was 69. He had ptosis of the eyelids, epicanthal folds, hypertelorism, large prominent and low-set ears, downturned corners of the mouth, micrognathia, short neck with torticollis to the left, right hemihypertrophy and micropenis (Fig. 1).

Chest X-rays revealed thoracic hemivertebrae and fused ribs (Fig. 2). Torticollis and hemihypertrophy were considered to be due to these skeletal abnormalities. The ECG showed cardiac dextroversion. The EEG was within normal limits. Dermatoglyphics revealed elevation of the axial triradius (t'). No simian crease was noted. Finger-tip patterns were 2 ulnar loops (thumbs) and 8 whorls.

Routine laboratory investigations revealed no abnormalities: red blood cell counts $515 \times 10^4/\text{cmm}$, hemoglobin 14.4 g/dl, hematocrit 40.0%, white blood cell counts 8,400/cmm, thrombocyte counts $32.0 \times 10^4/\text{cmm}$, GOT 26 U., GPT 9 U., total cholesterol 156 mg/dl, ZTT 33 K.U., TTT 4 K.U., LAP 157 U., γ -GTP 4 U., alkaline phosphatase 24 U., LDH 526 U., serum protein 7.0 g/dl, albumin 64.2%, α_1 4.9%,

Fig. 3. Q-stained karyotype of the propositus. Arrow indicates deletion of the short arm of chromosome 18.

Fig. 4. G-stained partial karyotypes of the propositus. Arrow indicates chromosome 18 with partial deletion of the short arm (18p1103→pter).

α_2 12.7%, β 8.2%, γ 10.0%, IgG 720 mg/dl, IgM 105 mg/dl, IgA 75 mg/dl, and calcium 10.2 mg/dl.

CYTOGENETIC FINDINGS

A cytogenetic study was performed on blood cultures from the patient and his parents with our routine methods. The Q-staining method was that described by Caspersson *et al.* (1970) and as a G-band technique, trypsin-Giemsa was employed with modifications (Nakagome *et al.*, 1973; Abe *et al.*, 1975). Conventional Giemsa staining disclosed that the propositus and his parents had a modal chromosome number of 46 chromosomes. Q- and G-banded karyotypes of the propositus revealed that the short arm of chromosome 18 was deleted with the break point within the band 18p11 about three-tenths of the length from the proximal border of the band (18p1103) (Paris Conf., 1971, 1975) (Figs. 3 and 4). Thus, the patient's karyotype was interpreted as 46,XY,*del*(18)(p1103→pter). No abnormal banding pattern, such as deletion of the short arm of chromosome 18 or duplication of other chromosomes was observed in the karyotypes of either parents.

DISCUSSION

Two important problems are often discussed in regard to the 18p— syndrome: one is the variation in the break point within the short arm of chromosome 18, and

therefore is the variation related to the extent of the deletion of the short arm. Q- and G-banded karyotypes in the present case exhibited a partial loss of one-third of the short arm with the break point at the band 18p1103 (Paris Conf., 1975). On the other hand, in the case reported by Johnson and Bachman (1976) and maybe in those of Uchida *et al.* (1965) and de Grouchy *et al.* (1967) the break occurred at the band 18p1100. Faust *et al.* (1976) stated that the break point within the band 18p11 varied from case to case in their 4 cases of 18p— syndrome.

The second is that the syndrome induces a broad variety of clinical signs, which have been well documented (de Grouchy, 1969; Faust *et al.*, 1976): the common ones are low birth weight, physical and mental retardation, facial dysmorphism, microcephaly and arhinencephaly, muscular hypotonia, short neck, broad chest, and clinodactyly. The features of facial dysmorphism include round flat face, hypertelorism, ptosis, epicanthus, large prominent and low-set ears, broad-based nose, carp mouth, abnormality of teeth (caries), cleft palate, and microretrognathia (Reinwein *et al.*, 1968; de Grouchy, 1969; Faust *et al.*, 1976).

Our patient fulfilled many of these diagnostic criteria of the 18p— syndrome. He also had thoracic hemivertebrae, fused ribs on the chest X-ray and micropenis. Funnel chest or broad chest has been described in some cases (Reinwein *et al.*, 1968; de Grouchy, 1969), but not thoracic hemivertebrae, fused ribs or micropenis.

Although the 18p— syndrome has a variety of clinical features, the phenotypic expression of these malformations does not correlate well with the extent of the deletion of the short arm of chromosome 18 (de Grouchy, 1969; Faust *et al.*, 1976). The expression of less frequently observed anomalies was therefore explained by the pseudodominance effect of recessive mutant genes located in the hemizygous state on the short arm of chromosome 18 (Uchida *et al.*, 1965). Another explanation is the hypothesis of gene-dose compensation postulated by Faust *et al.* (1976).

A decrease of IgA was also occasionally observed (Smith, 1976), but our patient had normal IgA and no serological abnormalities. Smith noted that the parental ages were 31.3 years for the mother and 35.7 for the father. Our patient's mother was 32 years old and his father 38.

Acknowledgment The authors express their sincere appreciation to Prof. Okuda for reviewing the manuscript.

REFERENCES

- Abe, T., Morita, M., Misawa, S. and Takeda, K. 1975. Fundamental studies on the G-staining procedures of human chromosomes. *Jap. J. Clin. Pathol.* **24**:141–144 (in Japanese).
- Caspersson, T., Zech, L., Johansson, C. and Modest, E. J. 1970. Identification of human chromosomes by DNA binding fluorescent agents. *Chromosoma* **30**: 215–227.
- de Grouchy, J., Lamy, M., Thieffry, S., Arthuis, M. and Salmon, C. 1963. Dysmorphie complexe avec oligophrenie: Deletion des bras courts d'un chromosome 17–18. *C. R. Acad. Sci. (Paris)* **256**: 1028–1029.
- de Grouchy, J., Rossier, A. and Joab, N. 1967. Une nouvelle observation d'aberration chromosomique 18p—. *Ann. Génét.* **10**: 221–223.

- de Grouchy, J. 1969. The 18p—, 18q—, and 18r syndromes. *In* Birth Defect. Original Article Series, Vol. 5, The National Foundation, New York, pp. 74–87.
- Faust, J., Hagedank, M. and Nieuwenhuijsen, C. 1976. The 18p— syndrome: Report of four cases. *Eur. J. Pediatr.* **123**: 59–66.
- Johnson, G. and Bachman, R. 1976. A 46, XY, *del* (18) (pter→p1100:) cebocephalic child from a 46, XX,t(12;18) (18pter→18p1100:: 12qter→12pter) normal parent. *Human Genet.* **34**: 103–106.
- Nakagome, Y., Iinuma, K. and Taniguchi, K. 1973. Points of exchanges in a human No. 5 ring chromosome. *Cytogenet. Cell Genet.* **12**: 35–39.
- Paris Conference (1971): Standardization in human cytogenetics. 1971. Birth Defects. Original Article Series, Vol. 8, No. 7, The National Foundation, New York.
- Paris Conference(1971), Supplement(1975): Standardization in human genetics. 1975. Birth Defects. Original Article Series, Vol. 11, No. 9, The National Foundation, New York.
- Reinwein, H., Struwe, F. E., Pettecken, F and Wolf, U. 1968. Defizienz am kurzen Arm eines Chromosoms Nr. 18(46,XX,18p—): Ein einheitliches Missbildungssyndrom. *Wochenschr. Kinderheilk.* **116**: 511–514.
- Smith, D. W. 1976. 18p— syndrome. Mental and growth deficiency ptosis or epicanthal folds, prominent auricles. *In* Recognizable Patterns of Human Malformation, W. B. Saunders, Philadelphia, pp. 28–29.
- Uchida, I. A., McRae, K. N., Wang, H. C. and Ray, M. 1965. Familial short arm deficiency of chromosome 18: Concomitant with arhinencephaly and alopecia congenita. *Am. J. Human Genet.* **17**: 410–419.