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PARTIAL 18 TRISOMY SYNDROME RESULTING FROM PATERNAL 6/18 RECIPROCAL TRANSLOCATION[1]

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Summary A female infant with distal 18q trisomy, confirmed by G- and Q-banding was reported. Her karyotype was 46,XX,-6,+der(6), t(6;18)(18qter→18q21::6p24 or 25→6pter)pat. She had the following clinical stigmata: hypertelorism, coloboma, bulbous nose with shallow nasal bridge, high arched palate, small chin, folds of redundant nuchal skin, hemangioma and limited abduction of the hip joints.

INTRODUCTION

In addition to the regular type of 18 trisomy (Edwards *et al.*, 1960), cases with trisomy for the long arm of chromosome 18 resulting from reciprocal translocation have been sporadically reported. Among them there are two types of 18q trisomy. One type is accompanied by typical features of 18 trisomy such as a prominent occiput, clenched fists with overlapping fingers, a narrow pelvis and rocker bottom feet (Hecht *et al.*, 1963; Rohde *et al.*, 1963; Gagnon *et al.*, 1963; Uchida *et al.*, 1964; Freiman and Wilton, 1967; Meyer-Robisch and Schwanitz, 1967; Gleissner *et al.*, 1970; Chesler *et al.*, 1970; Eriksson *et al.*, 1971; Cohen *et al.*, 1972; Goto *et al.*, 1973). The other type is not accompanied by them (Van Wijk *et al.*, 1961; Brodie and Dallaire, 1962; Valdmanis *et al.*, 1967; Rudd and Lamarche, 1971; Orye and Van Caster, 1972; Jenkins *et al.*, 1974). Recent banding techniques have enabled us to identify the trisomic part of each case. We report a case of distal 18q trisomy (18qter→q21) due to a paternal 6/18 translocation, whose clinical manifestations were much milder than those of regular 18 trisomy.

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CASE REPORT

The proposita was born as a first child of a 26-year-old mother and a 29-year-old father. There was consanguinity on the mother's side, *i.e.* the mother's parents were second cousins. The mother had no miscarriages but 3 siblings of the father were stillborn. The pregnancy was uneventful, however, the delivery was induced with oxytocin at 39 weeks of gestation because of the contracted pelvis. Apgar score was 5 and resuscitation was necessary. At birth, weight was 2,700 g, body length 43 cm and head circumference 32.5 cm. She had frequent episodes of cyanotic attacks and mild generalized tonic convulsions during neonatal period. She could not suck milk adequately and the rest of the required amount was administered through a nasogastric tube. When she was transferred to our hospital at 74

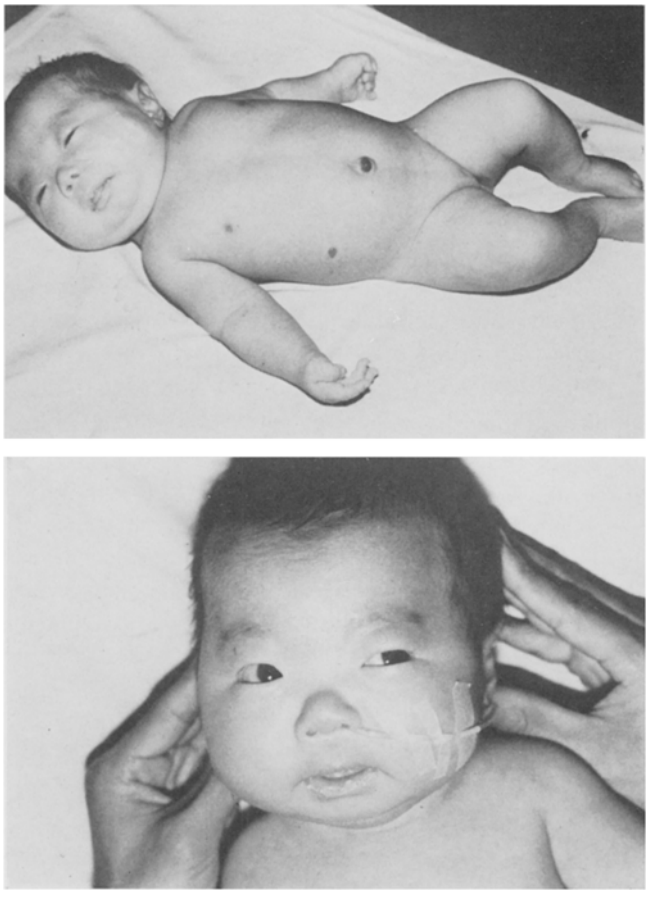

Fig. 1. The proposita.

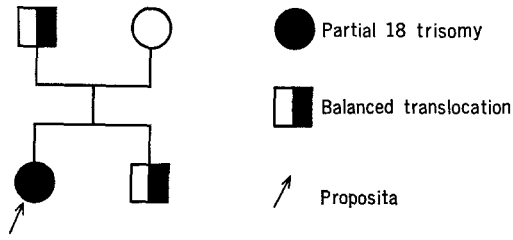

Fig. 2. Pedigree of the family.

days of age, she weighed 4,080 g. Her abnormal findings included: slight hypertelorism, coloboma of the left iris, atrophy of uveae and optic nerves, bulbous nose with shallow nasal bridge, high arched palate, small chin, husky crying voice, folds of redundant nuchal skin, hemangioma in the right abdominal flank and limited abduction of the hip joints (Fig. 1). Dermatoglyphics were unfortunately not available. The pedigree of the family is shown in Fig. 2.

Laboratory findings

Routine blood count, urinalysis and feces were normal. Hypogamma-globulinemia was demonstrated by electrophoresis. Electrocardiogram and electromyogram were within normal limits. Roentgenogram of the skull showed shallow sella turcica. Roentgenogram of the chest, the abdomen and the extremities revealed no abnormalities.

Clinical course

She showed slight failure to thrive and developmental delay. She had stridor and developed frequent respiratory distress because of glossoptosis, especially while she was asleep. She finally died of such an apneic attack at 195 days of age. Autopsy permission was not granted.

Cytogenetic findings

Cytogenetic studies were performed on blood cells from the proposita and her parents. Metaphases were obtained by the standard leukocyte culture technique. The Q-staining method was that described by Caspersson *et al.*(1970) with a minor modification (Misawa *et al.*, 1975). As a G-band technique, trypsin-Giemsa was employed with modifications (Abe *et al.*, 1976). Conventional Giemsa staining revealed that the proband's karyotype was 46,XX,Cp+. The same marker chromosome was found in the father. Q- and G-banded karyotypes of the father revealed a reciprocal translocation between chromosomes 6 and 18 with break points at 6p24 or 25 and 18q21, respectively (Fig. 3). Partial karyotypes from the proband and her father are shown in Fig. 4. Therefore, patient's karyotypes could be described as 46,XX,−6,+der(6),t(6;18)(18qter→18q21:: 6p24 or 25→6qter)pat.

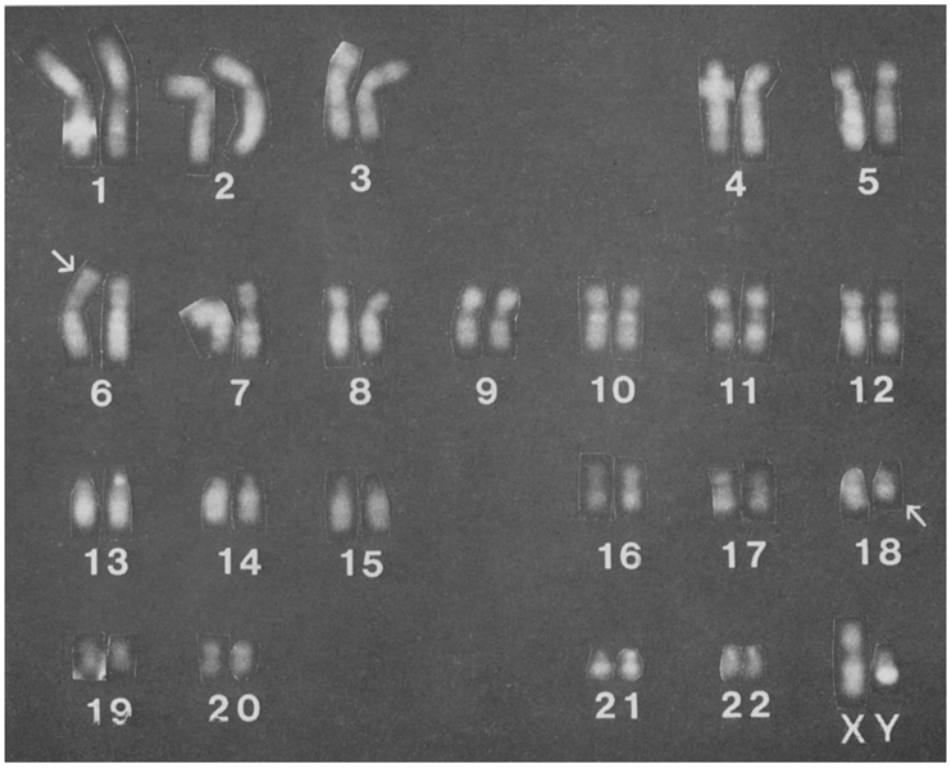

Fig. 3. Q-banded karyotype of the father.

DISCUSSION

In the trisomy 18 syndrome, the majority of reported cases are regular 18 trisomy but there are other subtypes such as partial trisomy (translocation trisomy), isochromosome, +i(18p) and +i(18q) (Miller *et al.*, 1965), mosaicism and double chromosomal anomalies. In 1961 Van Wijk reported the first case of E trisomy resulting from a reciprocal translocation. In our case, the long arm of chromosome 18 was translocated to the short arm of chromosome 6. Partial 18 trisomy derived from the translocation involving chromosomes of C group is rare and only 5 cases have been reported, that is, t(6;18) (p;q) Orye and van Caster, 1972; t(6;18) (q;q) Goto *et al.*, 1973; ins(11;18) (p15;q11q21) Chudley *et al.*, 1974; t(8;18) (p232; q123) Turleau and de Grouchy, 1977; t(12;18) (q24;q21) Fried *et al.*, 1978.

Rohde *et al.* (1964) described that long arm trisomy was accompanied by failure to thrive, hypertonicity, mental retardation, flexion deformity of fingers and congenital heart diseases, while short arm trisomy had mental retardation, low set ears and micrognathia. Eriksson *et al.* (1971) speculated that the phenotype of 18

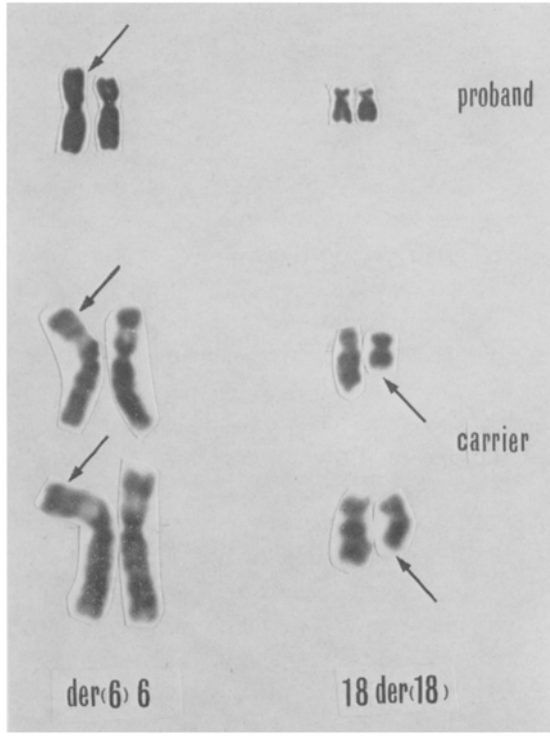

Fig. 4. Non-banded and banded partial karyotypes of the proband and her father (carrier). Arrows in the G-banded karyotypes of the carrier indicate breakage at the chromosome band 18q21 and reunion at the chromosome band 6p24 or 6p25, respectively.

trisomy is produced only when the long arm is completely triplicated. Since banding techniques have been introduced to identify chromosomes, several authors reported cases of 18 trisomy with the exact trisomic parts. Fried *et al.* (1978) described that trisomy for the distal one third of the long arm of chromosome 18 is not necessary to produce Edwards' syndrome.

Turleau and de Grouchy (1977) compared their own four cases of partial trisomy with several reported cases and concluded as follows: 1) Pure 18p trisomy does not have very characteristic phenotypes (Tangheroni *et al.*, 1973; Condron *et al.*, 1974; Nielsen *et al.*, 1974; Balíček *et al.*, 1976; Ogata *et al.*, 1977). Common clinical features are psychomotor retardation, chubby face, low set ears, small triangular mouth, narrow high arched palate, flat nasal bridge, micrognathia, scoliosis, fairly normal dermatoglyphics and absence of distal flexion creases on the fingers. 2) Distal 18q trisomy which they called "trisomy 18qter," has the region 18qter→18q22 (Castel *et al.*, 1975; Neu *et al.*, 1976; Vianna-Morgante *et al.*, 1976; Niazi *et al.*, 1978). This syndrome is accompanied by anomalies such as high-bossed

forehead, receding hair line, poorly indicated angles of the mandible, high arched palate, abnormally implanted teeth, normally set but posteriorly rotated ears with poorly folded helix, folds of redundant skin in the neck, narrow depressed chest, hernia, large hands with short fingers, abnormally implanted toes, typertonia of the limbs and excess of arches in dermatoglyphics. Visceral malformations are rare. The syndrome is accompanied by slight growth retardation, variable mental retardation and unimpaired life span. Compared to complete 18 trisomy, however, distal 18q trisomy syndrome does not show the following characteristic features of complete 18 trisomy which includes considerable growth retardation at birth, low set ears, clenched fists with overlapping fingers, severe inner organ malformation, narrow pelvis, rocker bottom feet and very short life span. They considered that the critical segment resulting in 18 trisomy syndrome locates on 18q11 and the region is responsible for most signs in this syndrome (Stern and Murch, 1975; Dziekanowska *et al.*, 1976; Kameyama *et al.*, 1977; Hodes *et al.*, 1978; Fried *et al.*, 1978).

There were a few cases which were not compatible with Turleau's postulation. Steele *et al.* (1974) reported two siblings in one family who had trisomy for the distal half of the long arm of chromosome 18. Although the q11 region was not triplicated, one of them had characteristic features of Edwards' syndrome. On the other hand, Chudley *et al.* (1974) reported three family members who did not show typical features in spite of triplication of the q11 region. However, it seems acceptable that q11 is the critical region in 18 trisomy syndrome.

The karyotype of the proposita was 46,XX,−6,+der(6),t(18qter→18q21::6p24 or 25→6qter)pat. According to Turleau's definition, the proposita belongs to the distal 18q trisomy syndrome because the chromosomal pattern was trisomic for 18q without the q11 region and she did not have characteristic features of 18 trisomy syndrome.

Subsequently, the mother became pregnant with the next child and amniocentesis was carried out. The chromosomal examination revealed balanced reciprocal translocation, being identical with the father's karyotype. The child was born phenotypically normal.

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REFERENCES

Abe, T., Morita, M., Misawa, S., Sawai, K., and Takeda, K. 1976. Fundamental studies on G-staining procedures of human chromosome (in Japanese). *Jap. J. Clin. Pathol.* **24**: 141–144.

Baliček, P., Žižka, J., and Lichý, J. 1976. An isochromosome of the short arms of the no. 18 chromosome in a mentally retarded girl. *Clin. Genet.* **9**: 192–196.

Brodie, H.R., and Dallaire, L. 1962. The E syndrome (trisomy 17–18) resulting from a maternal chromosomal translocation. *Can. Med. Assoc. J.* **87**: 559–561.

Caspersson, T., Zech, L., Johansson, C., and Modest, E.J. 1970. Identification of human chromosomes by DNA-banding fluorescent agents. *Chromosoma* **30**: 215–227.

Castel, Y., Rivière, D., Nawrocki, Th., Le Fur, J.M., and Toudic, L. 1975. Trisomie partielle 18q par translocation familiale t(18q−;13q+). *Lyon Méd.* **233**: 211–217.

Chesler, E., Freiman, I., Rosen, E., and Wilton, E. 1970. Congenital aneurysm of the membranous ventricular septum associated with partial trisomy E syndrome. *Am. Heart J.* **79**: 805–810.

Chudley, A.E., Bauder, F., Ray, M., McAlpine, P.J., Pena, S.D.J., and Hamerton, J.L. 1974. Familial mental retardation in a family with an inherited chromosome rearrangement. *J. Med. Genet.* **11**: 353–366.

Cohen, M.M., Finch, A.B., and Lubs, H.A. 1972. Trisomy 18 with an E/G translocation [46,XY, 21−,t(21q18q)+] identification of the component chromosomes by several laboratory techniques. *Ann. Génét.* **15**: 45–49.

Condron, C.J., Cantwell, R.J., Kaufman, R.L., Brown, S.B., and Warren, R.J. 1974. The supernumerary isochromosome 18 syndrome (+18pi). In: *Birth Defects: Original Article Series X*, No.10, pp. 36–42.

Dziekanowska, D., Dziuba, P., and Sobański, T. 1976. The trisomy 18 syndrome with an E/G translocation. *Hum. Genet.* **31**: 347–349.

Edwards, J.H., Harnden, D.G., Cameron, A.H., Crosse, V.M., and Wolff, O.H. 1960. A new trisomic syndrome. *Lancet* **1**: 787–789.

Eriksson, B., Fraccaro, M., Hultén, M., Lindsten, J., Thorén, C., and Tiepolo, L. 1971. Structural abnormalities of chromosome 18 II-two familial translocations, B/18 and 16/18, ascertained through unbalanced forms. *Ann. Génét.* **14**: 281–290.

Freiman, I. and Wilton, E. 1967. Trisomy 16–18 in the Bantu. *S. Afr. Med. J.* **10**: 558–561.

Fried, K., Bar-Yochai, A., Rosenblatt, M., and Mundel, G. 1978. Partial 18 trisomy (with 47 chromosomes) resulting from a familial maternal translocation. *J. Med. Genet.* **15**: 76–78.

Gagnon, J., Archambault, L., Laberge, É., and Katyk-Longtin, N. 1963. Trisomie partille 18 par insertion ou translocation 4/18. *Union Méd. Can.* **92**: 311–319.

Gleissner, M., Schwanitz, G., and Rott, H.D. 1970. Partielle Trisomie E18 (E18q−) als Folge einer balancierten Translokation D/E bei der Mutter. *Monatsschr. Kinderheilkd.* **118**: 441–444.

Goto, A., Komiya, H., and Matsui, I. 1973. 18 trisomy syndrome (in Japanese). *J. Pediatr. Pract.* **36**: 935–945.

Hecht, F., Bryant, J., Arakaki, D., Kaplan, E., and Gentile, G. 1963. Trisomy-18 syndrome due to *de-novo* translocation. *Lancet* **1**:114.

Hodes, M.E., Cole, J., Palmer, C.G., and Reed, T. 1978. Clinical experience with trisomies 18 and 13. *J. Med. Genet.* **15**: 48–60.

Jenkins, E.C., Weed, R.G., and Sandstrom, M.McH. 1974. An additional case of partial trisomy 18. *Ann. Génét.* **17**: 45–48.

Kameyama, J., Tsurusawa, M., Nakano, H., Shimizu, S., Okuda, R., Morita, M., and Abe, T., 1977. Trisomy for the long arm of the chromosome 18 due to *de novo* 18/21 translocation. *Jap. J. Hum. Genet.* **22**: 11–15.

Meyer-Robisch, M. and Schwanitz, G. 1967. Familiäre D/E-Translokation. *Acta Genet. Med. Gemellol.* **16**: 365–375.

Miller, J.Q., Rostafinski, M.J., and Hyde, M.S. 1965. A defective extra chromosome associated with clinical 17–18 trisomy syndrome. *Pediatrics* **36**: 135–138.

Misawa, S., Takino, T., Sugishima, K., and Abe, T. 1975. Quinacrine-banding analysis of the Philadelphia chromosome from five patients with chronic myelogenous leukemia. *Acta Haematol. Jap.* **38**: 307–310.

Neu, R.L., Ortega, C.C., Barg, G.A., Pinto, W., Gardner, L.I., Howell, W.M., and Denton, T.E. 1976. Inclusion of satellites in an 18/21 translocation chromosome shown by ammoniacal-

silver staining (sat-banding) in case of partial trisomy 18. *J. Med. Genet.* **13**: 520–522.

Niazi, M., Coleman, D.V., and Saldaña-Garcia, P. 1978. Partial trisomy 18 in a family with a translocation (18;21) (q21;q22). *J. Med. Genet.* **15**: 148–151.

Nielsen, J., Hreidarsson, A.B., Berggreen, S., Ried, E., Tsuboi, T., and Saldaña-Garcia, P. 1974. A mentally retarded male with karyotype 47,XY,+mar=?i(18p). *Ann. Génét.* **17**: 129–133.

Ogata, K., Iinuma, K., Kamimura, K., Morinaga, R., and Kato, J. 1977. A case report of a presumptive +i(18p) associated with serum IgA deficiency. *Clin. Genet.* **11**: 184–188.

Orye, E., and Van Caster, A. 1972. Familiaire partiële trisomie 18. *Acta Paediatr. Belg.* **26**: 41–52.

Rohde, R.A., Lee, A., and Sapin, S. 1963. A new trisomy-translocation chromosome (long arm E/E). *Lancet.* **2**: 1309–1310.

Rohde, R.A., Hodgman, J.E., and Cleland, R.S. 1964. Multiple congenital anomalies in the E1-trisomy (group 16–18) syndrome. *Pediatrics* **33**: 258–270.

Rudd, N.L. and Lamarche, P.H. 1971. Gene deletion and duplication effects on phenotype and gamma globulin levels. *J. Med. Genet.* **8**: 97–106.

Steele, M.W., Pan, S., Mickell, J., and Senders, V. 1974. Trisomy for the distal half of the long arm of chromosome No.18. *J. Pediatr.* **85**: 827–829.

Stern, L.M., and Murch, A.R., 1975. Pseudohermaphroditism with clinical features of trisomy 18 in an infant trisomic for parts of chromosomes 16 and 18: 47,XY,der(18), t(16;18) (p12;q11) mat. *J. Med. Genet.* **12**: 305–307.

Tangheroni, W., Cao, A., and Furbetta, M. 1973. Multiple anomalies associated with an extra small metacentric chromosome: modified Giemsa stain results. *Humangenetik* **18**: 291–295.

Turleau, C., and de Grouchy, J. 1977. Trisomy 18qter and trisomy mapping of chromosome 18. *Clin. Genet.* **12**: 361–371.

Uchida, I.A., Wang, H.C., Laxdal, O.E., Zaleski, W.A., and Duncan, B.P. 1964. *Cytogenetics* **3**: 81–96.

Valdmanis, A., Pearson, G., Siegel, A.E., Hoeksema, R.H., and Mann, J.D. 1967. A pedigree of 4/18 translocation chromosomes with type and countertype partial trisomy and partial monosomy for chromosome 18. *Ann. Génét.* **10**: 159–166.

Van Wijk, J.M.A., Tijdink, G.A.J., and Stolte, L.A.M. 1961. A case of partial trisomy. *Lancet* **2**: 1454.

Vianna-Morgante, A.M., Nozaki, M.J., Ortega, C.C., Coates, V., and Yamamura, Y. 1976. Partial monosomy and partial trisomy 18 in two offspring of carrier of pericentric inversion of chromosome 18. *J. Med. Genet.* **13**: 366–370.