Trisomy 13 Syndrome in Chinese Infants

Clinical Findings and Incidence*

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The syndrome of trisomy 13 was originally described by Patau *et al.* in 1960, and was recently reviewed by Taylor (1967, 1968). While at least 221 cases of trisomy 13 have been found (Magenis, Hecht, and Milham, 1968), only a few cases have been reported in oriental populations (Nair, Mathai, and Thankam, 1965; Nair and Vimala Nayar, 1965; Konishi *et al.*, 1966). Clinical screening for congenital anomalies of 25,814 consecutive Chinese newborn babies in the city of Taipei (Emanuel *et al.*, in preparation), over a period of 36 months, uncovered four cases of trisomy 13 proven by chromosomal analysis. Trisomy 13 syndrome has not previously been reported from Taiwan.

Case Reports

Birth characteristics of Cases 1-4 are included in Table I.

Case 1. The father of this baby (Fig. 1) had renal tuberculosis since 1962 and was thought to be recovered by 1966. During those 5 years, the following radiological studies were done: a plain film of the abdomen, three intravenous pyelograms, and retrograde pyelography once. He was treated with a combination of streptomycin, INH, and PAS. There were three normal sibs. The mother was healthy and the prenatal course was uneventful. Routine chest films comprised the only maternal x-ray exposure.

Received 16 September 1969.

* This investigation has been supported in part by the following sources: U.S.P.H.S. Training Grant 5-T1-AI-206 from the National Institute of Allergy and Infectious Disease; a General Research Support Grant (FR-05432) from the U.S. Public Health Service; a grant from the Brown-Hazen Fund of the Research Corporation; funds provided by the Bureau of Medicine and Surgery, Navy Department, Washington D.C.: work unit MR005.20-0165; Public Health Service Research Career Development Award K3-HD-31696 from the National Institute of Child Health and Human Development.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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The infant had multiple anomalies. The head had narrow temples and a slightly sloping forehead. Marked cyanosis with petechiae was noted over the frontal area. The forehead was hairy, the eyelids were tightly closed with an upward 'mongoloid' slant, and the eyes were small. The ears were small and deformed with marked

Fig. 1. Case 1, showing cleft lip with cleft palate and sloping forehead.

foldings of the upper helices. The nose was symmetrically flattened above a wide central cleft lip which extended upward to the nasal septum. A 2 cm. wide central cleft palate extended the entire length of the hard and soft palates. The neck was short without webbing. Nipples were widely spaced, and a grade 2-3/6 systolic murmur was audible along the left lower sternal border. The external genitalia were normal but the perineal body was small. Limitation of hyperabduction of the hips

TABLE I
BIRTH CHARACTERISTICS OF THE CASES

	Case 1	Case 2	Case 3	Case 4
Birth date	1/67	4/67	10/67	10/67
Sex	F	F	M	M
Gestation (wk.)	37	35	36	36
Birthweight (g.)	2400	1900	1700	1650
Birth length (cm.)	47	—	42	40
Placenta weight (g.)	400	—	490	490
Head circ. (cm.)	28.7	28.2	27.0	25.7
Maternal age (yr.)	43	30	26	26
Paternal age (yr.)	42	31	30	30
Previous pregnancies (total)	6	3	2	2
Previous foetal deaths	3	1	0	0
Age at death	24 hr.	8 dy.	30 hr.	14 hr.

was present. Mild rockerbottom feet and bilateral fibular polydactyly were present. Moderate hirsutism was noted over the back and shoulders. The Moro reflex was absent and her cry was weak and short. The infant had respiratory distress at birth, and died 24 hours after birth.

Case 2. The parents and two sibs of this child (Fig. 2) were normal and healthy. The prenatal course was

FIG. 2. Case 2, showing cleft lip with cleft palate, polydactyly, ulnar deviation of hands, and typical facies.

uneventful. The father had had yearly chest films, the mother had had no x-ray exposure.

The head had narrow temples. The anterior fontanelle was 2.5×2.5 cm. wide and the posterior fontanelle was 1.5×1.5 cm. The eyes were not small. The ears were small and low set. The nose was small and symmetrically flattened up to the nasal bridge. A central cleft lip extended upward to the border of the nasal septum. A central cleft palate 1.5 cm. in width involved the entire length of the hard and soft palates. A grade 3-4/6 systolic murmur was audible along the left lower sternal border and across the back. The external genitalia were normal, apart from a polyp 0.5×0.5 cm. which was visible in the vestibule. Ulnar deviation with ulnar polydactyly of both hands was found. Both feet had a slight rockerbottom defect, but there was no posterior protrusion of heels. The hips were normal, but the muscular development of both legs was poor. There was moderate hirsutism over the neck and shoulders. The Moro reflex was present but her cry was feeble. The infant died of pneumonitis at 8 days of age.

Case 3, Twin A. The third trimester was complicated by eclampsia. The father had had one chest film. The mother had had no x-ray exposure.

The physical examination revealed the following findings. The anterior fontanelle was 1.5×1.5 cm., the sutures were open, and the posterior fontanelle was a finger tip in size. There was a slanting forehead, and the shape of the head was moderately trigonocephalic. There was apparent hypertelorism and the palpebral fissures were small. There were no other eye defects. There was microtia with atresia of the auditory meatus on the right; the left ear was normal. Both ears were low set. There was a central cleft lip. The nose was wide and flat. A very small nasal septum was present. An incomplete cleft of the hard and part of the soft palate was present, but the uvula was intact. The neck was normal. The heart and lungs were normal.

The sex of the baby was indeterminate (Fig. 3). A very short shaft was embedded in fatty tissue. The urethra opened from the centre of the end of this structure. A small amount of shaft could be palpated. The labia were fused and very slightly scrotalized. There was no vaginal opening. No testes could be palpated, and there were no structures in the inguinal canal. The hips were normal, as were other joints. There was rudimentary ulnar polydactyly of the left hand. A four-finger line was broken just centrally to the radial end. The fingers were tightly flexed but not overlapping. The fifth finger was of normal length and had two flexion creases. The thumb was not retroflexible and the finger-nails were not hyperconvex or narrow. The right hand had all of the above findings except for polydactyly.

There was fibular polydactyly of both feet, and partial syndactyly of the third and fourth toes of the right foot. The feet were flat and there was slight posterior protrusion of both heels.

The Moro reflex was weak, tone was very poor, and the cry was weak. There were petechiae of the chest,

arms, and legs. Dyspnoea increased progressively, and the patient died at 30 hours of age.

Necropsy findings. The brain weighed 232 g. and the two cerebral hemispheres were symmetrical; convolutions and sulci were normal. The heart weighed 11 g. and the great vessels were normal. The ductus arteriosus was closed. The lungs together weighed 38 g. and had focal atelectases. Liver and spleen were not remarkable. There was a short, 1.3×0.2 cm. brownish appendage on the antimesenteric aspect of the ileum, proximal to the ileocaecal valve. The appendix was on the left but was not otherwise remarkable. The sig-

was lined by stratified squamous epithelium. The ovaries were represented by fibrous elements. Cells contained small oval nuclei and sparse cytoplasm, and had a laminated appearance. The leptomeninges and spinal cord were normal. The pituitary gland was hyperaemic and included a single cyst lined by stratified squamous epithelium, a remnant of Rathke's pouch.

Case 4, Twin B. Twin B (Fig. 4) had physical findings identical to twin A except that both ears were normal. The patient died at 14 hours of age with progressive dyspnoea. Necropsy findings were not significantly different from those of twin A.

FIG. 3. Case 3, twin A, showing malformation of external ear, polydactyly, and indeterminate external genitalia.

FIG. 4. Twin B, showing cleft lip with cleft palate, polydactyly, typical facies, and indeterminate genitalia.

moid colon descended in the right pelvis. The kidneys and adrenal glands were unremarkable. A long tubular structure, apparently the uterus, was present between the rectum and bladder, with the umbilical vessels coursing along its anterior aspect. Fallopian tubes were also present. Neither testes nor ovaries were grossly identified.

Microscopical examination revealed bilateral bronchopneumonia. The liver was moderately congested and extramedullary haematopoiesis was apparent in the sinusoids. The uterine cavity was lined by columnar epithelium and glands. The stroma was compact. Stratified squamous epithelium lined the external cervical os. The end of the small phallus contained the urethral meatus and a rich vascular bed. The vagina

Placenta. This pair of twins had two separate placentas. Combined weight of both placentas was 490 g. and they were of approximately equal size. The placentas were not attached at any point. There were two cords, each centred in the middle of its placenta, with three major vessels to each cord. Each placenta was continuous, with its own chorionic membrane, and the inner surface of each was covered by an amniotic sac.

Cytogenetic Results

Chromosomal analyses were made from short-term cultures of peripheral leucocytes by a modification of the micromethod of Arakaki and Sparkes (1963) (Table II). The karyotypes were interpreted as representing

TABLE II
CYTOGENETIC RESULTS, TRISOMY 13

Case	No. of Chromosomes per Cell						No. of Cells Counted	No. of Cells Karyotyped	Karyotype
	43	44	45	46	47	48			
Case 1				2	92	1	95	10	47,XX,D +
Case 2				71	1		72	14	46,XX,D - ,t(DqDq) +
Mother of Case 2	1		1	18			20	9	46,XX
Father of Case 2			2	18			20	7	46,XY
Case 3			29	30	1		30	5	46,XY,D - ,t(DqDq) +
Case 4			30				30	5	46,XY,D - ,t(DqDq) +
Mother of Cases 3 and 4		1	28				29	11	45,XX,D - ,D - ,t(DqDq) +
Brother of Cases 3 and 4		1	3	31			35	5	46,XY
Sister of Cases 3 and 4		2	25				27	7	45,XX,D - ,D - ,t(DqDq) +
Father of Cases 3 and 4			2	26			28	5	46,XY

47,XX,D +, in Case 1, and D trisomy with D/D translocation in Case 2 [46,XX,D - ,t(DqDq) +], and in the twins [46,XY,D - ,t(DqDq) +] (Fig. 5a).
Chromosome studies of the twins' family showed that the father and one sib had normal karyotypes. The

FIG. 5a. Partial karyotypes showing Group D and the t(DqDq) in the cases of trisomy 13 syndrome.

mother and female sib, born in 1962, had a modal number of 45 chromosomes (Fig. 5b); two members of the D group were missing and the large metacentric chromosome, presumably representing a translocation between these chromosomes, was again present [45,XX,D - ,D - ,t(DqDq) +]. They were considered to be balanced carriers of a t(DqDq).
The parents of Case 2 had normal karyotypes.

Other Investigative Studies

The dermal patterns of Cases 3 and 4 were identical, and were described by direct examination with magnify-

ing glass. The axial triradii were distal on both palms, and a four-finger line was broken just centrally to the radial side. The index and 5th fingers of both hands had radial loops, all other fingers had ulnar loops. Examination of the feet was unsatisfactory.
Haemoglobin starch block electrophoresis on Cases 1, 3, and 4 revealed foetal haemoglobin of approximately 100% in all cases and a trace amount of Hb-γ4 in Case 1, but Hb-Gower 2 and Hb-γ4, described by Huehns *et al.* (1964) in this syndrome, were not detected in Cases 3 and 4.
Complete blood typing of the twins and their parents showed no deletion effect in the propoiti. The blood types of both twins are identical and the probability that they are monozygotic was estimated to be 98%.

Discussion

The clinical findings in these four Chinese cases are comparable to those summarized by Taylor (1967, 1968) for other ethnic groups. Frequent findings in other reports which were not found in these children included capillary haemangiomas, hyperconvex finger-nails, and colobomata. The twins showed no heart defect on necropsy, and while the other two cases were not brought to necropsy, loud murmurs were heard. Thus, the diagnosis of trisomy 13 in Chinese infants can be strongly suspected on clinical grounds. The appearance of these children is similar in Caucasian,

FIG. 5b. Partial karyotypes showing Group A, t(DqDq), and Group D in the mother and sister of the twins with translocation trisomy 13.

Chinese, and Negroid populations (Cornu *et al.*, 1968).

In addition to the abnormalities usually associated with trisomy 13, the twins also had ambiguous external genitalia, a uterus, gonads represented only by fibrous elements, and an XY karyotype. Boys with the trisomy 13 syndrome frequently have minor genital abnormalities, primarily cryptorchidism (Taylor, 1967; Warkany, Passarge, and Smith, 1966), while girls may have bicornuate uteri, abnormal Fallopian tubes, and hypoplastic ovaries (Warkany *et al.*, 1966). Recently, a child with trisomy 13 and XX karyotype was also found to have streak gonads (Toews and Jones, 1968). Therefore, both male and female children with trisomy 13 have now been found to have varying degrees of hypoplasia of the gonads as well as other associated genital malformations.

These genital abnormalities in children with an excess of chromosome 13 suggest the possibility that the genes involved may be located on this chromosome. It may be of interest that cases of pure gonadal dysgenesis have been reported with large satellites on a D-group chromosome (Brøgger and Strand, 1965). Hamerton (1968) has reviewed the evidence that in other animal species, autosomal genes may interfere with gonadal development. Such a mechanism could explain the aetiology of the genital abnormalities in male and female cases of trisomy 13.

Huehns and associates (1964) and Powars, Rohde, and Graves (1964) independently reported that the level of Hb F was abnormally high in young infants with the trisomy 13 syndrome. In addition, Huehns and co-workers (1964) noted the presence of other haemoglobins (Hb-Gower 2 and Hb- γ 4) in the newborn with this syndrome. Hb F was found to be abnormally high in the three tested cases, and Hb- γ 4 in one (Case 1), but no Hb-Gower 2 was detected. Huehns suggested that the increases in Hb- γ 4, Hb F, and Hb-Gower 2 could all be interpreted as a specific retardation of normal maturational changes seen with these haemoglobins. Walzer *et al.* (1966) suggested that since both Hb F and Hb- γ 4 contain γ -chains, an increase in Hb F is evidence of an increase in γ -chain production. This, in turn, might result in the presence of increased amounts of Hb- γ 4.

In pooled U.S. data, 31 of 221 known cases of trisomy 13 syndrome had translocations (Magenis *et al.*, 1968; Hecht *et al.*, 1966). Of these (5.9%), 13 were D/D translocations involving centric or near centric fusions, and in only two instances were the translocations known to be carried by a parent. In our series of three pregnancies, two

involved D/D translocations, one of which was carried by the mother. While only a small series is involved, the present data suggest the possibility of ethnic group differences in translocation frequency. On the other hand, there seem to be no ethnic group differences in the frequency of translocations in Down's syndrome (Huang *et al.*, 1967; Tonomura *et al.*, 1966).

Table III summarizes the incidence data for trisomy 13 available from five large studies. The incidence rate in Taipei is 0.12/1,000 births (1 in 8,605). This is identical to the rate in one of the

TABLE III
INCIDENCE OF TRISOMY 13

Reference	Location	No. of Cases	No. of Births	Incidence per 1,000 Births
Smith (1964)	Wisconsin	2	10,345	0.19
Conen and Erkman (1966)	Ontario	5	134,325	0.04
Taylor and Moore†	England	2	9,688	0.21
Taylor and Fraser	England	11	94,000	0.12
Roberts†	Taiwan	3*	25,814	0.12
Present study				
Total		23	274,179	0.084

* Twins counted as one case.

† Unpublished observations, cited in Taylor (1968).

English series, and is not significantly different from the other English, Canadian, and American series (Smith, 1964; Conen and Erkman, 1966; A. I. Taylor, unpublished observations; Taylor and Fraser Roberts, unpublished observations, cited in Taylor (1968)) (χ^2 for Poisson distribution = 0.3217, $0.7 < p < 0.5$).

Summary

This paper describes four cases of trisomy 13 syndrome in Chinese infants. Two cases occurred in identical twins. Stigmata in this series were similar to those previously described. In addition, the twins, who were of XY genotype, were of indeterminate sex, and had streak gonads. These genital abnormalities appear to be a part of the spectrum of findings in the trisomy 13 syndrome.

An increase in foetal hemoglobin was present in the three cases examined, haemoglobin Bart's was found in one of these cases, but haemoglobin Gower 2 was not detected.

The twins and one other case had a D/D translocation defect, one of which was carried by the mother, while the other child had a standard trisomy 13 karyotype.

These cases were detected in the Taipei Collaborative Study of Congenital Malformations over a three-year period, in which liveborn and stillborn

babies were screened for malformations. This represents an incidence of 0.12/1000 total births, which is in agreement with the incidence reported from Western countries.

The authors are grateful to Drs. R. Q. Blackwell and E. R. Giblett for haemoglobin analysis and blood typing, respectively; to Dr. C. L. Chen, National Taiwan University Hospital, for referring Case 1; to Dr. C. C. Huang, Provincial Taipei General Hospital, for Case 2; to Dr. C. C. Wu, MacKay Memorial Hospital, for Cases 3 and 4; to Miss C. C. Chen, Miss Martha Sun, and Mr. E. S. Huang for technical assistance and karyotypes. Especial thanks are due to Mrs. Magdalena Lee Hsu, Miss Ruth Huang, and Miss Jean Chiao for loyal and invaluable assistance in the Taipei Collaborative Study. Thanks are due to Drs. David Smith, Philip Fialkow, and Pierre Ferrier for review of the manuscript.

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