Deletion of Short Arm of No. 4 (4p-)— A Detailed Case Report

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Deletion of the short arm of one of the B (4-5) group of chromosomes (usually No. 5) is most frequently associated with the clinical features of the cri-du-chat syndrome (Lejeune *et al.*, 1964). Some children with a deleted B chromosome have, however, had clinical features of a very different kind from those of the cri-du-chat syndrome. It was thought that the deletion in this group might affect the larger, late replicating pair (No. 4) (German *et al.*, 1964; Miller *et al.*, 1966; Warburton *et al.*, 1967). In three of four cases this has been confirmed by autoradiography (Wolf *et al.*, 1965; Leão *et al.*, 1967; Giorgi, Ceccarelli, and Paci, 1965), but in a fourth case labelling could not be performed because the patient died before this technique became possible (Hirschhorn, Cooper, and Firschein, 1965). The clinical features of this case included defects of mid-line fusion (scalp, coloboma of one iris, cleft palate, hypospadias) as well as severe mental retardation and convulsions. Pneumoencephalography showed probable absence of the septum pellucidum.

Wolf *et al.* (1965) described a child with bilateral cleft lip and palate, hypertelorism, left cataract, and right-sided ectopia of the pupil. The child had convulsions and died at the age of 3½ years. There was severe mental retardation, and radiologically there was hydrocephalus. The facial appearance of this child was vaguely similar to that of the child described by Hirschhorn *et al.*, much modified, of course, by the presence of the cleft lip.

The case reported by Leão *et al.* (1967) was of an 8-month-old child with bilateral exophthalmos, beaked nose, facial asymmetry, hypospadias, and a systolic bruit. The facial appearance and the other clinical features in this child were not similar to the other cases but cytogenetically the deleted chromosome was a 4.

Giorgi *et al.* (1965) described a child who showed

gross hypomandibulism, with cleft palate, hypertelorism, beaked nose, talipes, slanting eyes, low set ears, and a systolic murmur. The child died at 32 days but the chromosome analysis had already demonstrated the deletion of the short arm of a 4th chromosome. Clinically, the most obvious feature was the extreme degree of micrognathia and the beaked nose.

We present here a further case with deletion of the short arm of a B group chromosome in whom the clinical features were certainly not those of the cri-du-chat syndrome but did not correlate closely with those of the case described by Giorgi *et al.* (1965). Autoradiography confirmed the deleted chromosome as being one of the late replicating (4th) chromosome pair.

Case History

This child, born April 1968, was the third child of a mother of 28, and a father of 30, who were unrelated. No drugs or illnesses were recorded in early pregnancy. Birthweight 3 kg. Admission on day of delivery as ? hydrocephalus. Marked hypotonia, feeble cry, skull flat on top and posteriorly with a bulging forehead; head circumference 34.25 cm. Fontanelle flat but large. Small scalp defect posterior to anterior fontanelle. No clinical hydrocephalus. The facial appearance was extraordinary with the flat top to the skull and the marked protrusion of the forehead (Fig. 1). The degree of micrognathia was that of the Pierre Robin syndrome, but the upper part of the face was not consistent with this diagnosis. In profile the forehead made the chin even more obviously receding (Fig. 2). The nose was squashed rather than beaked, but the eyes were more prominent than usual. The right eye had a fixed pupil, the left had an ectopic pupil. The optic fundi were normal. Other than this the abnormalities were few, though the child was generally abnormal, with feeble cry, marked hypotonia, failure to suck, and lack of spontaneous movement. A hairy naevus in the lumbar region and the dorsiposed digits 2, 3, and 4 on the right foot were the only other findings, until a systolic murmur appeared and the child went into uncorrectable heart failure leading to death at 3 months of age. The child was tube fed all her life, and she showed no signs of

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FIG. 1.

FIG. 2.

FIG. 1. Facial appearance, showing the flat top to the head, frontal bossing, and extraordinary facies. The left ectopic pupil can probably just be seen.

FIG. 2. Facial appearance in profile to show the severe degree of hypomandibulism. The ears are not low set. The flat top to the skull is again evident.

development. She never smiled, she could not focus, and she did not respond to tactile stimuli; she gave all the appearances of being grossly mentally retarded. Her weight gain was poor and she gained only 1.2 kg. in 3 months, in spite of our tube feeding her nutritional requirements.

Routine investigations. Hb 28 g./100 ml. falling to 18 g./100 ml. Electrolytes normal. Plasma urea 18 mg./100 ml., rising terminally to 78 mg./100 ml. WBC's 12,800/cu. mm., with a normal differential. Blood group O Rh positive. CSF—no WBCs; protein 20 mg./100 ml.

Radiological investigations. (a) *Mandible:* did not show such severe hypomandibulism as was apparent clinically. This is because no true lateral radiograph was obtainable and even small degrees of rotation will obscure mandibular hypoplasia. (b) *Skeleton:* centres of ossification were generally delayed and irregular when present. There was hypoplasia of the proximal phalanx of the 5th digit, as is found in the trisomy syndromes. Thoracolumbar kyphosis of slight degree. (c) *Renal tract:* non-functioning kidneys on IVP; (d) *Heart:* moderate cardiomegaly; (e) *CNS:* ventriculography showed a stage 2 hydrocephalus (Fig. 3) with an intact septum pellucidum.

Necropsy findings. There was a notably odd facies, mainly due to micrognathia, prominent orbital ridges, and bossing of the frontal/parietal bones.

Scalp: near the margin of the left parietal bone there was a scalp defect; sections of this area showed a defect of epidermal appendages suggestive of a fusion defect; this defect did not involve the meninges. **Palate:** complete central cleft hard and soft palate. **Brain:** externally the brain was normal but section showed mild hydrocephalus. **Heart:** ventricular septal defect 6 mm. in diameter and a foramen ovale 7 mm. wide; right ventricle was hypertrophied suggesting pulmonary hypertension of considerable degree; no pulmonary stenosis. **Bowel:** the ascending and transverse colons were suspended with the small bowel; descending colon had a normal course. Small bowel length normal.

Urogenital tract: striking changes. The external genitalia were normal female but there was no uterus. Instead two primitive Müllerian ducts came together at the vulva, though their lumina did not fuse (Fig. 4). At the other end they approached the bladder wall from where the left Müllerian duct ran as a solid core of tissue to a streak ovary containing very few primordial follicles. The right Müllerian duct became a uterine-like structure (lined with normal endometrium) with thickened muscular wall, the total diameter of which was 8 mm. This structure continued to a normal fimbria, then to a cystic ovary in which there were no primordial follicles (Fig. 5 and 6). The ureters were embedded in thick fibrous tissue on the posterior wall of the bladder. The right ureter was dilated because of this and there was a dilated renal pelvis and calyces as well: similar findings were present in the left kidney which also contained pus.

FIG. 3. Ventriculogram shows mild degree of hydrocephalus which was not under pressure, not progressive, and probably secondary rather than primary.

The eyes showed no abnormality other than the left coloboma.

Chromosome investigations. Cultures of peripheral leucocytes were set up on two separate occasions. The

first sample was harvested in the usual way, and an analysis of 30 well-spread metaphase plates showed the chromosome complement to be 46,XX,Bp-; i.e. there was an almost complete deletion of the short arm of one of the B (4-5) group (Fig. 7). The second sample, was, therefore, long labelled with tritiated thymidine (specific

FIG. 4. A diagrammatic representation of the internal genitalia showing Müllerian ducts which fused only at the vulva (A). The left duct (B) was solid and led to a streak gonad (F). The right duct enlarged to try to form a uterus and then via a normal fimbria was associated with a cystic ovary without primordial follicles.

activity 5 Ci/mM—0.3 μ Ci/ml.) for 5 hours before harvesting (Colcemid being added 3 hours before harvesting). Grain counts and long arm length measurements were made on a series of 17 labelled well-spread cells. In 16 out of the 17 cells the deleted chromosome was one of the more heavily labelled pair (Fig. 8). An analysis of length by the best pairing method showed (despite low differentials in chromosome length in this particular individual) that the deleted chromosome paired best with the longest most heavily labelled of the remaining 3 chromosomes (Table).

On the basis of the measurement and length data the deleted chromosome is one of the longer, later labelling pair, i.e. a deleted 4.

FIG. 5.

General view of left gonad to show small number of follicles.

FIG. 6.

Enlarged view to show that most of the gonad is stroma with few follicles.

Permission for chromosome analysis on both parents was twice refused.

TABLE
ANALYSIS OF VARIANCE OF LONG ARM LENGTH

Item	SS	df	MSS	VR
Between cells	198.70	16	12.42	34.5 ***
Between chromosomes	9.12	1	9.12	25.3 ***
12.75 for 3 df	1.62	1	1.62	4.5 *
Interaction cells × chromosomes	2.01	1	2.01	5.6 *
Total variation	17.14	48	0.36	
	228.59	67		

The undeleted chromosomes are classed as 1, 2 or 3 within each cell according to grain count.
1 = heaviest etc. *** = $p < 0.1\%$, * = $5\% > p > 1\%$.

Discussion

Similar cytogenetic findings are not always associated with similar clinical features but all the autosomal abnormalities described so far have been associated with severe mental and physical retardation. We are sure the case we have just described fits into this general picture, and we also feel sure that this child's clinical state was related to the chromosome abnormality. But is this just a collection of findings or is it a syndrome recognizable in others?

As a result of our experience with 7 confirmed personal cases of the cri-du-chat syndrome, we are quite certain, on clinical grounds, that this patient did not suffer from this condition. Other than the

mental and physical retardation there was no clinical similarity whatsoever. In addition, in all seven cases the deleted chromosome was a member of the smaller, earlier-labelling pair, i.e. deleted 5 (work in preparation for publication) whereas this patient had a deleted 4. In our series therefore there is a good correlation between the clinical features observed and the type of chromosome deleted.

If there is a 'deletion of short arm of 4 syndrome' then the 5 cases described to date with this cytogenetic finding should also have roughly similar and recognizable features. In 4 of the 5 there was a scalp skin dysplasia probably representing a fusion defect. In 4 of the 5 there were fusion defects of the palate. In 3 of the 5 there was an abnormality of the iris (or lens), hydrocephalus, micrognathia, and skeletal abnormality. In 2 of the boys there was hypospadias, and in our female patient a gross abnormality of development of the internal genitalia and ovaries, one of the latter coming into the category of 'streak' gonads exactly of the type which are known to occur in the infantile form of Turner's syndrome (Gordon and O'Neill, 1969). So, it seems likely that at this stage one could clinically suspect this syndrome in a grossly abnormal child with extreme hypoplasia of the mandible, abnormally shaped skull, grade 2 hydrocephalus, defects of iris or lens, cleft palate, congenital heart disease, and congenital abnormality of the genito-urinary tract in male or female, with, of course, failure to thrive both physically and mentally.

Fig. 7. Karyotype of the proband. Chromosome complement, 46,XX,Bp-.

FIG. 8. The B group of chromosomes from 5 cells showing the deleted chromosome to be one of the later labelling pair.

Any variation in the clinical picture, where the same chromosome is deleted, may be due to: (1) differences in the quality of the genetic loss from the deleted chromosome; (2) differences in the genes present in haploid dose; (3) hidden mosaicism, since only one tissue has been examined in most cases.

Any similarities in the clinical features between cases with deletion of different chromosomes may be due to: (1) partial homology between the short arms of 4 and 5; (2) the presence on chromosomes 4 and 5 of genes influencing the same system

at different points, such that disturbance in the genetic balance of either 4 or 5 leads to disruption of that system.

Despite these qualifications, there still seems to be good evidence that deletions of 4 and 5 lead to recognizably different clinical appearances. Including our series, 20 out of 23 cases of cri-du-chat show a deleted 5, and all 4 of the individuals with clinical features *inconsistent* with a diagnosis of cri-du-chat in which autoradiographic studies have been performed show a deletion of 4.

We would still, however, say that deletion of the

short arm of 4 is not such a well-established syndrome as that of deletion of the short arm of 5. Further work remains to be done before the case will be completely convincing.

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