A Translocation $t(Bq^+ : Cq^-)$ in a West Indian Family and a Report of a Second Family Showing a Possible Long Arm Group B Translocation

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Abnormalities of the long arms of the autosomes 4 and 5 (group B) have been reported fairly frequently in the past two years. Most are presumed to be the result of reciprocal translocations between a B and another autosome. As far as can be ascertained from the descriptions and photographs, where provided, the affected patients bear little resemblance to each other. This may be because either the chromosomes involved in the translocation differ in each case, or the amount of material exchanged varies. Many of the anomalies observed have been of a non-specific nature. Nevertheless, it is important to report the findings in such cases in the hope that a definite pattern of anomalies will emerge in some cases, leading to the identification of a distinctive syndrome such as the D and E trisomies, and deletions of chromosome 5 and 18. For this reason we report a family with a B-C translocation, which presented with an infant with many anomalies, dissimilar to those previously reported and with unusual findings. A second patient, phenotypically normal, with mosaicism of apparently a normal line and a minor stem line with an enlarged long arm of a B chromosome, is also described, because the latter abnormality appeared to be responsible for the occurrence of repeated abortions. Both families were of West Indian-African extraction.

Family A

The proband of this family, was delivered at term after a pregnancy complicated by hydramnios (9 l. approximately). He was limp and asphyxiated and weighed 2.7 kg. On examination at 1 day he was pink, but the following anomalies were noted: micrognathia, a right pre-auricular sinus, bilateral proptosis

(Fig. 1), a wide, slightly bulbous nose, and ears with abnormal helices. An area in the midline of the skull was deficient in skin and bone. The hands were held with medial deviation of the fingers. Oesophageal atresia was excluded by the passage of a naso-gastric tube.

He was admitted to hospital at 17 days of age because of continuous crying and shortness of breath. In addition to the above findings, mild icterus was observed, and a grade 2 systolic murmur was heard down the left sternal border. He was discharged from hospital at the age of 4 weeks and died at home at 5½ weeks.

FIG. 1.—Proband of Family A, at age 3 weeks.

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FIG. 2.—Liver, showing focal lesions (H. & E. $\times 20$.)

Family history. The baby was the product of the tenth pregnancy of Mrs. A., aged 36 years. All except the first of her children were by her husband, aged 34 years. The third child had died at the age of 6 months of gastroenteritis and the sixth pregnancy had terminated in abortion at 3 months' gestation. All the living children, aged from 15 months to 18 years, were examined and found to be physically and mentally normal.

Mrs. A. has two brothers aged 41 and 22 years, both alive and apparently normal. Her parents are both living. Her father, who is normal and healthy aged 64, has one sister aged 51 years with 4 normal children, none having died. The mother of Mrs. A., aged 59 years, is said to be afflicted by mental disease and loss of memory. Only Mrs. A.'s father consented to examination.

Pathological findings. Necropsy, 27 hours after death, showed the body to be that of a small, thin, negro infant weighing 2400 g. and measuring 47 cm. in length. The head circumference was 34.6 cm. The facial appearance was as previously described. The hands were held flexed in ulnar deviation but the palms were normal. The only external abnormalities were excessively prominent metatarsal heads and a quadrangular defect in the parietal bone just anterior to the posterior fontanelle.

Internally, gross abnormalities were an enlarged heart, weighing 28 g. (normal 21 g.), with a high ventricular septal defect 0.5 cm., and a small defect in the foramen ovale, and kidneys of normal size lying on the pelvic brim. The brain weighed 405 g. and showed dilatation of the third and lateral ventricles. The

external genitalia appeared normal though the testes were in the inguinal canals. There were 2 umbilical arteries.

Histological examination revealed numerous abnormalities. The *lungs* showed a moderate interstitial pneumonitis, of a chronic nature with minimal alveolar exudate. The *liver* showed a unique picture of widespread focal lesions of apparent degeneration with little inflammatory reaction and no central necrosis (Fig. 2): in addition there was extensive extramedullary haemopoiesis. In the *pancreas* there were perivascular foci of lymphocytes and eosinophils. The *kidneys* showed fairly extensive congenital glomerulosclerosis: the affected glomeruli were frequently associated with foci of cells resembling extramedullary haemopoiesis but with many eosinophils; there was also scattered nephrocalcinosis in the cortex. The *brain* showed foci of calcification and the arachnoid and pia subjacent to the parietal bone defect were thickened. A section of *costochondral junction* showed evidence of abnormal and retarded growth: there was extension of cartilage matrix into the trabeculae with bridging and banding, and poor ossification. The heart, adrenals, and testes were not remarkable.

Because of the cytogenetic findings in the family, Mrs. A. was advised to have no further children, but by the time she consulted a family planning clinic, she was already pregnant for the 11th time. In view of the fetal risks and the acute anxiety as to the outcome of the pregnancy, which she was experiencing, termination of pregnancy and sterilization was performed at 10 weeks' gestation, when a normal male fetus measuring 5 cm. in length was removed.

FIG. 3.—Karyotype of *propositus*, showing increased length of a long arm of a B chromosome: 46XY, Bq+ (arrowed).

Cytogenetic findings. Chromosome analyses were performed on the *propositus*, all the living sibs, the parents, grandfather, and the fetus obtained at hysterotomy. Peripheral blood was cultured by the microtechnique of Arakaki and Sparkes (1963). Flame-dried smears were stained with Giemsa.

From the fetus, explants of amnion, skin, lung, and kidney were grown in Leighton tubes for 5 to 12 days by the method of Basrur, Basrur, and Gilman (1963), exposed to hypotonic solution, fixed, and the coverslips stained with Giemsa.

In the *propositus*, all 30 cells examined showed 46 chromosomes, with a considerable increase in length of the long arm of one of the B autosomes (Fig. 3). No other abnormality was detected.

The mother, 2 sisters, and the maternal grandfather all showed the same anomaly of the B autosome, with, in addition, a missing autosome in group C and an extra autosome in group E, resembling a chromosome 16 or 17 (Fig. 4). This complex was assumed to be the result of a reciprocal translocation between part of a long arm of a B and the long arm of a C. The remaining sibs, the abortus, and the father had normal chromosome complements. Autoradiographic studies on Mrs. A. and also Mr. B. in the second family were unsuccessful, and it has not yet been possible to repeat them. We, therefore, suggest that the *propositus* was effectively partially deficient in the long arm of B autosome, and trisomic for part of the long arm of a C autosome. In view of the size of the B translocation chromosome,

FIG. 4.—Karyotype of a carrier sister, showing a translocation between long arms of a B and a group C autosome: $t(Bq+; Cq-1)$.

it seems that the partial trisomy was the more significant abnormality.

Family B

Mr. and Mrs. B., aged 30 and 24 years, respectively, were referred for cytogenetic investigation by Dr. T. P. Jupp because of recurrent abortions. Married since 1965, Mrs. B. had had 3 pregnancies, occurring in 1965, 1966, and 1967, which had miscarried between 8 and 10 weeks' gestation. She had reached the menarche at age 15 years and had menstruated regularly for 5 days every 28 days. Clinically she showed the presence of small intramural fibroids, but hysterosalpingography in 1965 and in 1966 showed no distortion of the uterine cavity. Otherwise she appeared to be perfectly normal and healthy. Hormonal estimations during pregnancy showed no evidence of progesterone deficiency. Mr. B. appeared to be a normal healthy male, 173 cm. in height. Seminal analysis showed 110,000,000 sperm/ml., with normal motility and appearance. He denied any extra-marital experience.

Family history. Mrs. B. was the second child of a family of 9, all of whom are alive and well. Her parents aged 50 and 44 years are also alive and well. There is no family history of congenital abnormality or abortion.

Mr. B., however, comes from a large family of which only 3 survive. An accurate history of the ages and cause of death of all the children was difficult to obtain because his mother was dead. His parents apparently had 12 children of which 3 are living. Mr. B.'s father, aged 56, appeared to be healthy but was a heavy drinker. He was the oldest of a family of 9, all except one being alive and well. The exception had died of 'rum' at the age of 35 years. Mr. B.'s mother died in 1962 at the age of 51 years, of hypertension. She was one of 9 children, 2 of whom had died in adult life, the rest being alive and well. There was no history of congenital abnormalities. The details of her pregnancies as far as could be ascertained are as follows.

(1) Male, died of a 'stroke' at age 15; he had a 'leaking heart' and had been subject to violent fits of temper. (2) patient; (3) male, died at 1½ years, cause unknown; (4) male, died at 1 year, cause unknown; (5) male, stillbirth; (6) abortion; (7) female, died at the age of 3 weeks, cause unknown; (8) abortion; (9) male, died at the age of a few weeks, cause unknown; (10) male, aged 24 years alive and apparently normal; no children (single); (11) female, aged 21 years, alive and normal, with 4 normal children. (12) Another abortion occurred somewhere between 1933 and 1950.

During the course of investigation of the family, Mrs. B. became pregnant for the fourth time. She aborted spontaneously on June 4, 1967, 7 weeks after her last menstrual period on April 15.

Pathology. The specimen consisted of a complete abortus with an intact sac and placenta, weighing 44.2 g. On opening the sac, the embryo was unfortunately cut. It was 2 cm. in length, with eyes and early limb buds, but the tissues were soft and friable suggesting maceration. Histological examination did not contribute any further information other than showing anlagen of the brain, eyes, and major viscera, and the tissues showed autolysis. Specimens were taken for tissue culture.

Cytogenetic examination. Specimens of blood were taken from Mr. and Mrs. B. and processed as in Family A. Explants from the skin and amnion of the abortus were grown in Leighton tubes by the method of Basur *et al.* (1963), but unfortunately only the amnion grew and the preparations were inadequate for chromosomal analysis. Thionine stain of the amnion showed the cells to be sex chromatin positive. Chromosome analysis of Mrs. B., Mr. B.'s father, brother, and sister, showed normal chromosome complements. Mr. B.'s blood, cultured on 2 occasions, showed mosaicism. Approximately 18.5% of cells had 46 chromosomes with an apparently unbalanced karyotype (Fig. 5),

FIG. 5—Karyotype of Mr. B. showing increased length of long arm of a B chromosome: 46XY Bq+.

with an enlarged long arm of a B chromosome almost identical to that seen in the propositus of Family A, though the increase in length was not quite so marked. The remaining cells showed a normal complement.

Discussion

It seems possible, in view of the family history of Mr. B., that his mother might have had a chromosome abnormality, possibly a reciprocal translocation involving a B chromosome, but in the absence of any information about the physical anomalies of Mr. B.'s sibs or chromosome studies in the mother, any attempt to define the abnormality would be pure speculation. The second point which arose was the possibility of double fertilization giving rise to Mr. B.'s 2 stem lines. Because of this, blood group studies were performed on Mr. B., his father, brother, and sister by Miss Marjory Stroup of the Ortho Research Foundation.

There was no evidence of a double population of red cells, though there was a weak reaction with anti-Jk^a which may have been due to the heterozygous nature of the cells. Another possible mode of origin of Mr. B.'s mosaicism is the one that was postulated by Hsu *et al.* (1967) for their patient, whose parents were normal. They suggested that a normal zygote experienced a non-disjunctional division involving an unknown autosome, which resulted in 3 types of cells, one monosomic, one trisomic, and one normal. The monosomic line would be lost because the cells would not be viable, and a subsequent translocation or insertion of the extra autosome into a B would result in the abnormality observed. They found one trisomic cell in their fibroblast culture to support this theory. However, it does imply 2 major genetic errors occurring. A third mode of origin would be a series of post-zygotic breaks and rearrangements resulting in some balanced and some unbalanced cells, similar to that occurring in the case of Turner, Bass, and Kaplan (1966), in which 3 types of cell were seen, 2 of which were balanced and 1 unbalanced. One of the balanced lines contained an acentric fragment which would presumably be unstable, the fragment being ultimately lost from the tissues as the patient gets older (Atkins, Sceery, and Keenan, 1966; Lüers, Struck, and Nevinny-Stickel, 1963).

The third point of clinical interest in Family B is whether the presence of the translocation in mosaic form could be responsible for the recurrent abortions. Clinically it was felt that though Mrs. B. had palpable fibroids, they were not encroaching on the uterine cavity and could probably be discounted as the cause of the miscarriages. That

the cytogenetic anomaly was responsible, could be proved by the demonstration of abnormalities at meiotic division or the finding of chromosomal abnormalities in the aborted material. Unfortunately the latter opportunity was missed because of the poor preservation of the abortus. Edwards *et al.* (1962) warned that one should be particularly cautious in relating an abnormal karyotype to abnormalities which are not generalized, congenital, and uncommon. This caution is well taken in this case, though several cases have now been described (Jacobsen, Dupont, and Mikkelsen, 1963; Lejeune and Berger, 1965) of families with repeated abortions showing reciprocal translocations. The problem arose in our case as to what the couple should be advised. It was suggested that they adopt a child, but at this stage, without certain proof of the culpability of Mr. B.'s mosaicism, they were not told to prevent further conception.

There are several points of interest in Family A. We have attempted to compare the propositus clinically and cytogenetically with other reported cases. As it is not certain in our case, as in many others, which of the chromosomes in groups B and C are involved, we have summarized the findings in both cases involving deficiency of the long arm of a B autosome (Table I) and cases of partial trisomy of the long arms of C autosomes (Table II). Cytogenetically, of the abnormalities of the long arm of a B, only the 6 cases shown are comparable. Of these, only the case of Trujillo *et al.* (1966) has any clinical features in common, and there are many anomalies not shared by both cases. The case described by Shaw, Cohen, and Hildebrandt (1965) might be considered the antithesis of our case, as the major cytogenetic abnormality was a duplication of the long arm of a B.

Similarly, when considering the abnormalities of a C autosome, only the cases shown in Table II are cytogenetically comparable. The only case which has clinical abnormalities in common with ours, is that of Punnett *et al.* (1966) which facially bears some resemblance. Unfortunately, we have no skeletal x-rays to compare the flaring of the epiphyses described in their patient.

No cases previously reported have the histological abnormalities seen in our patient, and it must be admitted that some of these may be entirely coincidental. The liver lesion appears to be most unusual and is difficult to explain aetiologically except as part of a viral infection or possibly a congenital anomaly. The interstitial pneumonitis and the lesions in kidneys, pancreas, and brain suggest a chronic infection such as rubella. We have seen identical

TABLE I
Cases with Abnormalities of Long Arm of a B Chromosome

Author	Age	Sex	Other Chromosome Involved	Comments
Arkins and Feingold (1967)	6 wk.	F	Unknown; parents normal	Similar to cri-du-chat
Bray and Josephine (1964)	5 mth.	M	" " "	Physically unlike our case
Gendel and Wasserman (1966)	11 mth.	F	" " "	Resembled trisomy 21
Hsu <i>et al.</i> (1967)	11 yr.	M	Unknown; mosaic, with a normal line and one trisomic cell E	Small, retarded, some features of trisomy 21
Trujillo <i>et al.</i> (1966)	1½ yr.	M	Unknown; parents normal	Most resembles our case.
Turner <i>et al.</i> (1966)	9 mth.	M	Mosaic with 3 lines, due to post-zygotic rearrangement; translocation between long arms of 2 B chromosomes	Features of cri-du-chat

TABLE II
Cases with Abnormalities of Long Arm of C Autosome

Author	Age	Sex	Other Chromosome Involved	Comments
Clarke <i>et al.</i> (1964)	7 yr.	F	C-3 translocation	Flaccid, retarded, seizures, webbing of neck, high palate, genu valgum, pes planus, short hands
Gray <i>et al.</i> (1966)	Newborn	M	G-C translocation	Bunched flexed fingers, low bat ears, cleft lip and palate. talipes, patent ductus, pyloric stenosis
Grouchy and Canet (1965)	1 yr.	M	D-C translocation	Mental retardation, low-set ears, mongol slant, hypertelorism, heart, eye, and kidney anomalies, hypoplastic genitalia
Jensen and Melchior (1967)	Newborn	M	" "	Cleft palate, broad nose, low-set ears, abnormal hands and feet, hypertrichosis, septal defect
Mann <i>et al.</i> (1965)	18 yr.	F	B-C or X translocation	Primary amenorrhoea
Punnett <i>et al.</i> (1966)	Newborn	M	18-10 translocation	Triangular head, low-set ears, high palate, naevi, overlapping toes, optic atrophy, splaying of epiphyses, cryptorchidism
Rohde and Catz (1964)	19 yr.	F	6-9 translocation	Mentally retarded, sexual infantilism, micrognathia, dry coarse skin, ectopic pupils, macroglossia, simian creases

lesions in the brain, kidneys, and pancreas in several cases of congenital rubella (Thorburn and Miller, 1967), but the pneumonitis in this case does not resemble that of rubella which has a characteristic alveolar exudate as well as an interstitial infiltrate. Without any serological or virological information, one can only speculate on the origin of this presumed infection. The lesion in the costochondral junction is assumed to be non-specific and related to growth retardation, both intra- and extra-uterine (Emery and Kalpaktsoglou, 1967) caused by the chromosome abnormality and the possible chronic infection.

The segregation of the cytogenetic abnormalities in this family are also of interest. In such a large family one might have anticipated finding all the possible results of a balanced translocation. Of

the 11 pregnancies of Mrs. A., only one is known to have had an unbalanced constitution, 2 had the carrier state, and 6 were normal. It is tempting to speculate that the one spontaneous abortion was due to an unbalanced state, either the same as that of the propositus or the alternative, a partial monosomy of a C autosome. Theoretically one would expect a 1:4 chance of normal offspring, assuming that the partial C monosomy is viable or 1:3 if not. There would be similar chances for the balanced translocation and a 1:2 or 1:3 chance of a severe abnormality. Mrs. A. appears to have been lucky compared with our other patient Mr. B., who has been unable to produce viable offspring. The origin of the translocation in Family A was presumably in the gametes of a grandparent of Mrs. A. or even further back.

Summary

Two patients with abnormalities of the long arm of a B autosome are described: an infant with multiple abnormalities, physical and histological, and a phenotypically normal adult male with a family history of high infant loss and the father of 4 abortions. In the first case the abnormality was due to a balanced translocation in the mother and grandfather, between a B and a C autosome. In the second case there was mosaicism, but the origin of the abnormality was not determined. The abnormalities in the first case are compared with other previous reports of abnormalities of C and B chromosomes, and the segregation of gametes in the family is discussed.

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