Short Arm Deletion of Chromosome 18

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A case is described of a girl with developmental retardation and facial anomalies.

A cytological abnormality was found consisting of a deletion of the short arm of one of the E chromosomes, which on the basis of morphologic and autoradiographic studies have been identified as a number 18 chromosome.

Autopsy findings included aplasia of the corpus callosum of the brain, congenital deformities of the cranial bones and of the chest.

The clinical and anatomical findings in 14 previously reported cases are discussed.

A considerable number of reports have now been collected dealing with the 'short arm deletion of chromosome 18 syndrome' since the initial recognition of this chromosomal abnormality by de Grouchy et al.1-8

Although the chromosomal aberration seems identical at least morphologically in all patients, no specific phenotype has emerged from various case reports. However, it might be expected that the loss of a sizeable chromosomal segment would have some specific effects upon the phenotype which would be of aid in the clinical recognition of the anomaly.

The purpose of this paper is to report a case which provides further evidence that certain clinical features may indeed be shared by individuals with a short-arm deletion of the number 18 chromosome, and to review the literature on this subject.

CASE REPORTS

The patient is a white female born in March 1965, as the first child of a 28-year-old mother and a 31-year-old father.

The couple had been unsuccessful in attempts to have children for the previous five years. Sterility investigation of the couple revealed that the mother was apparently normal, but that the father had a low sperm count. Neither the

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parents had been exposed to therapeutic irradiation, nor the mother had any x-rays performed during pregnancy.

Pregnancy had been complicated by significant ‘spotting’ during the first five months of gestation. The mother was treated with Delalutin*, 125 mg/week for the remainder of gestation. Hydro-Diuril†, 50 mg/day for two weeks and then 50 mg every three days, was used to relieve edema which developed in the fourth month of gestation. In addition, the mother received Eskatrol; for a short time within the first two months of gestation for the relief of ‘emotional stress’.

At approximately two months of gestation, the mother suffered from what appeared to be an acute attack of viral infection with symptoms of fever, nausea, vomiting and malaise. These symptoms persisted for approximately three to four days. At eight and one-half months of gestation, delivery was induced with pitocin. The 2.8 kg (six pounds 3 oz.) female infant had a somewhat peculiar face, a small appearing head with a slanting forehead, and close-set eyes with a fine lateral nystagmus.

Heart rate was 160/min, with no evidence of abnormal sounds or murmurs. The abdomen was soft, and no masses were palpable. Normal female genitalia were noted.

The child was discharged five days after birth, but was readmitted to the same hospital at two weeks of age because of respiratory and feeding difficulties.

Fig. 1. Peculiar face with hypotelorism of the eyes and asymmetrical appearing head with slanting forehead.

* Delalutin: Progesterone-17-caproate
† Hydro-Diuril: Hydrochlorothiazide
‡ Eskatrol: Dexedrine (dextroamphetamine sulfate) 18 mg and Compazine (prochlorperazine) 7.5 mg
X-ray examination of the skull and facial bones at this time revealed the calvaria to be small as compared with the face. There was also some loss of the normal contour of the brow. However, there was no definite gross abnormality present in either the skull or facial bones.

The child was admitted to the Department of Pediatrics, University of Louisville School of Medicine, Children’s Hospital, Louisville, Kentucky, at 15 months of age for evaluation of mental retardation (Fig. 1).

The patient was profoundly retarded. She had a peculiar face with hypotelorism of the eyes and an asymmetrical appearing head with slanting forehead. Weight was 6.8 kg (15 lbs) and height 71.1 cm (28 inches), both well below the 3rd percentile. Her ears were prominent and low-set. No cardiac, renal and gastrointestinal malformations were clinically evident. Electroencephalogram revealed a moderate generalized dysrythmia. Blood chemistries and complete blood counts were within normal limits.

Since the previous hospitalization the patient had suffered from repeated episodes of upper respiratory infections, several middle ear infections, and seemed to run a fairly constant low-grade fever of around 38.3°C (101°F), the etiology of which was never determined.

Development was obviously very slow with the patient and she was unable to hold her head steady without support and she just began to turn over from back to abdomen at fifteen months of age.

At nineteen months of age, the patient was again admitted to the hospital with

Fig. 2. Karyotype of a cell with deletion of the short arm of one chromosome of groups 17-18.
melena. The patient had numerous generalized grand mal type seizures in the hospital and expired on October 26, 1966.

**Pathological findings**

Gross anatomical diagnosis was as follows: 1) Congenital aplasia of the corpus callosum of the brain, 2) congenital deformities of the cranial bones, 3) congenital deformities of the chest cage, and 4) bronchopneumonia, bilateral (probably viral pneumonitis).

The cranium appeared somewhat elongated and asymmetrical and the left parietal bone was elevated. The chest was deformed with indentation of the inferior portion of the sternum, and there was an elevated area anteriorly over the right chest cage.

The brain was relatively heavy, weighing 609 g. Absence of the corpus
callosum was noted and the cerebral hemispheres were actually joined with no
intervening tissue present. The lateral ventricles were somewhat enlarged. They
were separated by only a thin zone of brain tissue. The cerebellum and the brain
stem were not remarkable. The pituitary gland was average in size.

Microscopic examination of the brain showed a rather marked increase in the
number of nuclei. In addition, considerable perivascular edema was noted through-
out the brain tissue.

Heart, kidney and gastrointestinal tract showed no evidence of congenital
anomaly.

Cytological studies

The patient’s peripheral blood leukocytes, as well as the parents’, were
cultured by the standard technique,\(^9\) using commercially available reagents.
Abnormalities were found only in the propositus, whose karyotype is shown in Fig. 2.
Analysis of the cells revealed consistent deletion of the short arm of one chromo-
some of groups 17–18. There was no other apparent chromosomal aberration.
Cytogenetic analysis of the parents’ leukocyte cultures were apparently normal.

Simultaneously, autoradiographic studies were carried out using the technique
described by Schmid,\(^10\) with minor modifications. Radioactive thymidine (Schwartz
Bio-research, Inc., Orangeburg, N.Y.) in final concentration of 0.5 μc/ml culture
medium was added six hours before the cultures were terminated. After four hours,
colchicine was added, the total time in tritiated-thymidine being six hours.

In all the intact cells studied the abnormal telocentric chromosome matched
the number 18 chromosome on the basis of its incorporation of tritiated thymidine
(Fig. 3). In a buccal smear, the sex chromatin was positive and the Barr body
appeared normal in size.

Dermatoglyphics

Dr. Irene A. Uchida kindly evaluated the dermal patterns of the digits, palms
and soles. However, there were no characteristic dermatoglyphic patterns in this
patient.

DISCUSSION

Although no complete autosomal monosomy has yet been discovered, several
‘partial’ monosomy conditions are found in patients with multiple anomalies. These
‘deletion’ syndromes now make up another group of chromosomal aberrations which
often allow viable but malformed offspring. They are: chromosome 4-partial
deletion of a short arm,\(^12,13\) chromosome 5-partial deletion of a short arm (cri-du-
chat syndrome),\(^14\) chromosome 18-partial deletion of a short arm\(^1-8\) and G\(_1\)–
chromosome partial monosomy of 21 (antimongolism syndrome).\(^15,16\) Among
them, the short arm deletion of number 18 chromosome apparently represents
quantitatively the smallest deletion.

In the present case, the abnormal chromosome resembles most closely the long
<table>
<thead>
<tr>
<th>Case</th>
<th>Father</th>
<th>Mother</th>
<th>Paternal age</th>
<th>Other phenotypic information</th>
<th>Physical examination</th>
<th>Intelligence</th>
<th>Subjective</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Male</td>
<td>Female</td>
<td>41</td>
<td>Male, Weight 60 kg, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>B</td>
<td>Male</td>
<td>Male</td>
<td>40</td>
<td>Male, Age 40, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>C</td>
<td>Male</td>
<td>Male</td>
<td>42</td>
<td>Male, Age 42, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>D</td>
<td>Male</td>
<td>Female</td>
<td>41</td>
<td>Male, Age 41, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Short stature, Weight 60 kg, Height 170 cm</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Table 1.** Summary of reported short arm deletions in a chromosome 17-18.
<table>
<thead>
<tr>
<th>Case C</th>
<th>Newborn</th>
<th>Female</th>
<th>±</th>
<th>Short 44 cm</th>
<th>Cebocephaly and hypotelorism</th>
<th>28</th>
<th>?</th>
<th>Mother mosaic Case A</th>
</tr>
</thead>
<tbody>
<tr>
<td>6) Hickox, cited by Uchida</td>
<td>4 yr.</td>
<td>Female</td>
<td>Low</td>
<td>Short</td>
<td>Hypotelorism, dental caries, and webbed neck</td>
<td>35</td>
<td>37</td>
<td>?</td>
</tr>
<tr>
<td>7) Lewis, Poulding and Woods</td>
<td>33 yr.</td>
<td>Male</td>
<td>35</td>
<td>Short 140 cm</td>
<td>Ptosis, low-set ears, micrognathia, micromelia, and cubitus valgus</td>
<td>41</td>
<td>?</td>
<td>Normal</td>
</tr>
<tr>
<td>8) Dill and Miller</td>
<td>21 mos</td>
<td>Female</td>
<td>Low</td>
<td>?</td>
<td>Anterior capsular cataract, dislocated hip, brachycephaly, and hypertelorism</td>
<td>28</td>
<td>31</td>
<td>?</td>
</tr>
<tr>
<td>9) Faint and Lewis</td>
<td>Newborn</td>
<td>Female</td>
<td>±</td>
<td>?</td>
<td>Cyclops, pituitary agenesis, and arrhinencephaly</td>
<td>30</td>
<td>34</td>
<td>?</td>
</tr>
<tr>
<td>10) Migeon</td>
<td>12 mos.</td>
<td>Male</td>
<td>50</td>
<td>Short 66 cm</td>
<td>Corneal opacity, Simian crease, talipes equinovarus, bilateral hip dislocation, inguinal hernia and microcephaly</td>
<td>32</td>
<td>31</td>
<td>Normal</td>
</tr>
<tr>
<td>11) Nitowsky et al.</td>
<td>Newborn</td>
<td>Female</td>
<td>±</td>
<td>Short</td>
<td>Cyclops</td>
<td>42</td>
<td>39</td>
<td>Normal</td>
</tr>
<tr>
<td>12) Present cases</td>
<td>20 mos.</td>
<td>Female</td>
<td>Low</td>
<td>Short</td>
<td>Aplasia of the corpus callosum, hypotelorism, deformities of the cranial bone</td>
<td>28</td>
<td>31</td>
<td>Normal</td>
</tr>
</tbody>
</table>
arm of a number 18 chromosome. In addition, the autoradiographic studies with tritiated thymidine indicates that it completes its DNA replication later than two other members of the 17-18 group. Previous studies of DNA synthesis in normal peripheral blood cultures have shown that the number 17 chromosome terminates DNA synthesis earlier than the number 18 chromosome.\textsuperscript{10,11} Therefore, on the basis of tritiated thymidine incorporation as well as morphology, the abnormal chromosome readily can be identified as number 18.

The latter chromosomal anomaly was first reported by de Grouchy\textsuperscript{1} in a 6-year-old mentally retarded male with hypertelorism, low-set ears, serrated teeth, proximal displacement of the thumbs, incurving of the 5th finger, syndactyly of the second and third toes and normal stature.

Since the original description, fourteen cases (including the case presented here), have been reported in the literature available to us. Table 1 shows a summary of reported cases of short-arm deletion of chromosome 18.

As has been pointed out previously by several authors, in contrast to the findings in the other partial monosomy syndrome, the cases described with a simple deletion of the short arm of 17–18 do not constitute a distinct clinical entity.\textsuperscript{7,8,17} One is impressed with the diversity in phenotypes associated with apparently the same chromosomal aberration.

Nitowsky et al.\textsuperscript{8} suggested that the diversities in phenotypes associated with this syndrome possibly result from heterogeneity in the types of underlying cytologic abnormality. Migeon\textsuperscript{7} also speculated on the presence of similar somatic characters associated with aberrations in different chromosomes and suggested that either similar genetic material was present at different genetic loci or, more likely, that the phenotype was common to more than one genotype. She also suggested that the diversities in phenotype might be caused by the expression of recessive alleles present in the hemizygous short arm.

However, in a recent publication Migeon\textsuperscript{7} summarized the common features shared by this group as follows:

1) Mental retardation, sometimes associated with gross cerebral defect, such as arhinencephaly and microcephaly, 2) short stature, (with the exception of the patient of Grouchy), 3) absence of cardiac, renal or gastrointestinal malformations, and 4) presence of a spectrum of minor congenital malformation, such as hypertelorism, micrognathia, strabismus, epicanthus, low-set ears, round face (frequently associated also with a deletion of the short arm of chromosome 5).

The patient reported by Van Dyke\textsuperscript{2} had many features associated with the syndrome of gonadal aplasia. The patient described by Migeon\textsuperscript{7} also had short stature, webbed neck, lymphedema, shield chest, and cubitus valgus, frequently identified with Turner’s syndrome and with X-chromosome monosomy.

In these cases, the possibility of an 18/X translocation cannot readily be dismissed. In our patient, however, neither evidence of gonadal aplasia nor Turner-like physique was observed.

In 1882 Kundrat described the relationship of malformations ranging from
simple arrhinencephaly to severe ethmocephaly. Cyclopia is the severest malformation, characterized by absence of the rhinencephalon, approximation of the cerebral hemispheres, union of ventricles, fusion of the basal ganglia, and defects of the corpus callosum, flax, and commissures. Less severe forms show either incomplete separation of the anterior portion of the hemispheres, partial callosal agenesis, or union by a plate of gray and white matter in the usual site of the corpus callosum. Alternatively, these anomalies may reflect failure of the development of midline structures in the developing brain.18

Since many case reports have shown that the trisomy 13–15 (D1) syndrome frequently is associated with facio-cerebral malformations, it is of interest that at least four of 14 cases with short arm 18 deletion have a rare type of dysmorphogenesis of the mid-face and brain.19–22 Furthermore, two of four cases with facio-cerebral malformation showed cyclopia.

In our case, it appears that no appreciable amount of chromosome material from a number 18 has been translocated to any of the other chromosomes. The presence of a normal karyotype in both parents suggests that the abnormal chromosome arose during gametogenesis or during an early cleavage division of the zygote.18

In the reports so far published, the prenatal history was not recorded or was normal in the majority of cases, and no references were made to either maternal ingestion of drugs or complications during gestation.

Ten of the 14 patients whose sex was mentioned were female. This female sex predominance might be explained by a greater prenatal fatality rate of male zygotes with partial 18 monosomy.

Advanced parental age was associated with at least four of the patients. However, it is impossible with so few cases at this point to determine whether this chromosomal abnormality is age dependent.

Acknowledgment

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References