Partial deletion 8q without Langer-Giedion syndrome: a recognisable syndrome

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SUMMARY We report two de novo cases of del(8)(pter→q24.1:) with breakpoints involving the distal part of band 8q24.1. The clinical features were similar and there were no obvious stigmata of Langer-Giedion syndrome (LGS). There are three other cases reported with a deletion of chromosome 8 at approximately the same breakpoint, one without LGS and some similarities to our cases, the other two with LGS. Our findings would support the observation that the critical segment for the assignment of LGS is proximal to or involves the proximal part of 8q24.1, but a review of published reports suggests that the aetiology of LGS may be a more complex issue.

Deletions of the long arm of chromosome 8, whether interstitial or terminal, have been of considerable interest over the past few years in ascertaining an association with Langer-Giedion syndrome (LGS) or trichorhinophalangeal syndrome type II (TRP). The first terminal deletion of chromosome 8 (q24) was reported by Beighle et al.4 when they described an infant with multiple congenital abnormalities without apparent clinical evidence of LGS. In 1980, Buhler et al.5 reported the first case of a chromosome abnormality with LGS and a presumed terminal deletion of 8q24. In the light of the later association of del(8)(q23) with LGS reported by Turleau et al.6 and supported by Fryns et al.,7 Buhler et al.5 reinvestigated their case along with an additional case in 1983 and confirmed their assignment to 8q24.2→qter with 8q24.3 as the putative band for LGS.

In 1984 we reported two cases of apparent terminal deletions of chromosome 8 at 8q24.1 with no obvious stigmata of LGS at that time.8 We report in more detail here a follow up of those cases and cytogenetic findings in support of the view that the critical assignment of LGS may be proximal to our breakpoint in the middle of band 8q24.1 at approximately 8q24.12→q24.13. Since our initial report, however, Buhler and Malik7 have reinvestigated their cases and reviewed a number of other reports. They have reassigned the critical segment for LGS to part of band 8q24.1 adjacent to q23, which would support our findings.

Case reports

Case 1

Case 1 is the second child of unrelated, 26 year old parents. The prenatal period was uneventful and she weighed 2540 g after a normal delivery at 36 weeks’ gestation. The mother has moderately severe asthma and the father has hay fever. The three year old sister is normal.

At three days she acquired staphylococcal conjunctivitis which was slow to respond to treatment. At seven weeks she was admitted to hospital with feeding difficulty and failure to thrive. She was noted to be floppy with a rounded face, hypoplastic mid face, shallow orbits, and prominent eyes. The nasal bridge was wide, the nostrils anteverted, and the philtrum long. Weight and length were below the 3rd centile, occipitofrontal circumference on the 10th centile, and inner canthal distance above the 97th centile (fig 1).

She fed very poorly and weight gain remained slow. She had persistent nasal obstruction but no choanal atresia. At two months of age she developed a severe wheezing illness resembling bronchiolitis. During the next six months she was admitted to hospital on many occasions with episodes of moderate or severe asthma, during some of which she required intensive care. At the age of four months, during a severe wheezing illness, she...
developed intractable rectal prolapse and required rectoplasty and a sigmoid colostomy which has now been closed. At seven months she had severe measles. From the age of six months she has been on regular nebulised beclomethasone and salbutamol and on this treatment has not had further severe asthmatic attacks. She has, however, had several episodes of acute otitis media.

During her illnesses in the first six months of life several brief tonic convulsions were noted. However, at three years seven months no further fits had occurred and she was not taking anticonvulsants. At this age she showed retardation, functioning around the 12 month level in all fields of development. Her weight was on the 25th centile, height between the 3rd and 10th centiles, and head circumference on the 50th centile. She had been supplied with hearing aids for a partial hearing loss with both conductive and sensorineural components.

Investigations
Extensive investigations failed to find a cause for her failure to thrive and developmental delay, other than the chromosomal abnormality. Serum immunoglobulins at four months showed a low serum IgG at 1.64 g/l, which had risen to 4.07 g/l at 17 months. Other immunoglobulins were normal. An EEG at five months and skeletal development at three years seven months were normal. A CT brain scan showed a moderately dilated ventricular system with increased cortical subarachnoid spaces and interhemispheric fissures.

CASE 2
Case 2 is the fourth child of unrelated parents, the father aged 33 and the mother 30 years. The pregnancy and birth were normal. There are three other healthy children. He presented aged 26 months with a febrile convulsion. Initial investigations, including a lumbar puncture, were normal. This was followed, within a month, by another non-febrile fit. The EEG showed a post central slow wave excess. On the basis of the history carbamazepine was started. Four months later, during an attack of left otitis media, four further seizures occurred. A single drop attack in a non-febrile interlude was noted. One year after initial presentation, an episode of status epilepticus occurred and he has had multiple admissions for status epilepticus.

On presentation the findings were as follows: height 25th centile, weight 75th centile, and head circumference 97th centile. He had a round face with a wide nasal bridge and a mongoloid slant to the eyes; there were Brushfield spots. The inner intercanthal distance was above the 97th centile. There was a poorly controlled latent divergent squint. The philtrum was long and the mouth carplike. The ears were simple (fig 2). At the age of five, he developed left sided pes cavus. X ray of the lumbar and sacral spine showed the last lumbar vertebra to be sacralised and bifid. At operation, the only abnormal finding was a moderately tight filum, which was divided. Psychological assessment suggested a global delay to the 24 to 30 month level at a chronological age of three years 11 months.

FIG 1 Appearance of case 1 at six months.

FIG 2 Appearance of case 2 at 26 months.
Investigations
The following investigations were found to be abnormal. Four EEGs showed a progressive deterioration, the last showing minor status epilepticus. The bone age was delayed being two years eight months at a chronological age of three years three months. IgM was low (0.3 g/l) but IgA and IgG were normal. The serum calcium showed a gradual fall to 2.0 mmol/l for which no cause could be found. Treatment with vitamin D reversed this. A CT scan showed the ventricles to be at the upper limit of size for his age with a more prominent subarachnoid space than usual. The cortical sulci were prominent. Laboratory tests including skin biopsy (light and electron microscopy) were normal. Skeletal examination at five years 11 months showed no evidence of multiple exostoses associated with LGS.

Materials and methods
CYTOGENETIC STUDIES
Cytogenetic studies of cases 1 and 2 were performed on peripheral blood lymphocytes and skin fibroblast cultures using standard culture techniques. High resolution GTG and RBG banding was performed on case 2. Cytogenetic analysis was undertaken on the parents of both probands.

Results
Cytogenetic analysis showed similar breakpoints in both cases, the karyotypes being 46,XX and 46,XY,del(8)(pter-q24.1) respectively. The deletions had occurred in the middle of band 8q24.1 and although the banding was not of sufficient quality to show band 8q24.12, the results suggest that the most likely breakpoint for both cases is 8q24.13. Both were presumed to be terminal deletions and these observations were confirmed with RBG banding. The parents of both probands had normal chromosomes, thus indicating that the deletions were de novo (figs 3 and 4).

The clinical findings are compared with the reports of Beighle et al and Buhler et al in the table for cases with breakpoints near 8q24. Our cases have few similarities to the two LGS cases of Buhler et al.

Discussion
In our opinion, the two cases reported represent part of a broad spectrum of abnormality related to 8q deletions, ranging from lethal to clinically normal. There is no reported evidence associating spontaneous abortions with this deletion, which suggests that there might well be a larger number of patients undiagnosed in the earlier years of life. Our two patients are now four and six years old and neither has multiple exostoses considered diagnostic of LGS. Although our patients have a long philtrum, the shape of the nose and general facial appearance would differentiate them from the TRP phenotype. A third case not reported here involving an interstitial
TABLE Abnormal findings in three reported cases of patients with del(8q24) and in the two present cases

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Beighle et al</th>
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* = LGS syndrome <3% short stature, <3% microcephaly.
† = global retardation, ‡ = after photostimulation, § = reassignment of breakpoints from original publications in 1984.

deletion at 8q24.2→q24.3 (Schwarz et al., unpublished data) also does not show obvious signs of LGS.

The survival and prognosis of patients with a chromosome deletion at 8q24.1 is difficult to assess in view of the paucity of published reports involving this breakpoint. Bowen et al reported an 18 year old, intellectually normal male with characteristics of LGS with an interstitial deletion at 8q24.11→q24.12 in addition to an apparently balanced de novo translocation t(2;9)(q21;ql3). They concluded that a deletion in the region 8q24.11→q24.12 was sufficient to produce the LGS and that patients with larger deletions may also manifest mental retardation and other anomalies. Their results would be in agreement with our own cases where the breakpoints appear to be halfway down band 8q24.1, making 8q24.13 in both our cases the most likely breakpoint and thus excluding LGS. A complex rearrangement involving a deletion of 8q24.11→q24.13 in a patient with LGS has recently been reported by Schwartz et al. Fryns and Van den Berghe detected an interstitial deletion of 8q24.12 in TRP I in a 10 year old, mentally normal boy.

The recent communication by Buhler et al has defined a possible shortest region of overlap between reported cases of 8q deletion and LGS as being 8q24.11→q24.13. The comparison of our two cases with other published cases would support our current opinion that the critical chromosome seg-
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ment for LGS is proximal to, or only just involves, the proximal part of band 8q24.13. Our cases would, therefore, represent a new syndrome.

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References


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