Congenital cutis laxa with retardation of growth and development

M A Patton*, J Tolmie†, P Ruthnum‡, S Bamforth‡, M Baraitser*, and M Pembrey*

From *the Department of Clinical Genetics, Institute of Child Health, 30 Guilford Street, London WC1N 1EH; †Departments of Paediatrics and Clinical Genetics, Royal Hospital for Sick Children, Yorkhill, Glasgow; and ‡Department of Medical Genetics, University Hospital of Wales, Heath Park, Cardiff.

SUMMARY Seven patients with congenital cutis laxa are presented. The associated features include developmental delay, joint laxity, wide anterior fontanelle, growth retardation, dental caries, and osteopenia. The heterogeneity and inheritance of congenital cutis laxa are discussed. This particular syndrome appears distinct and is likely to be autosomal recessive in view of the two brother-sister sib pairs in this report.

Congenital cutis laxa is a rare disorder characterised by loose, redundant skin present at birth. The condition is heterogeneous. One form of congenital cutis laxa has been reported by Agha et al in association with intrauterine and postnatal growth retardation together with developmental delay, delayed closure of the anterior fontanelle, and ligamentous laxity. Previous reports have predominantly been in girls and it has been suggested that this condition may represent an X linked dominant. We report seven new cases including two brother-sister sib pairs suggesting that autosomal recessive inheritance is more likely.

Case reports

CASE 1 (PEDIGREE A, FIG 1)
This male child was born at 34 weeks' gestation to a non-consanguineous Scottish couple. The father was 17 and the mother was 23 years old. The mother had a healthy boy and girl from a previous marriage. His birth weight was 2·2 kg (3rd to 10th centile). Loose skin was noted at birth. During the first year, developmental delay became evident and his length, weight, and head circumference fell below the 3rd centile for age.

On examination there was redundant lax skin, especially over the buttocks and thighs, with generalised ligamentous laxity and poor muscle bulk. There was lax facial skin and a facial appearance which included a prominent nose, long philtrum, telecanthus, and an antimongoloid slant of the palpebral fissures (fig 2).

Normal investigations included a skeletal survey, an echoencephalogram, a renal ultrasound examination, EEG, and prometaphase chromosome analysis. Over the next year he made slow developmental
Congenital cutis laxa with retardation of growth and development

progress and his growth continued parallel to but below the 3rd centile. At two years of age he could just walk unsupported and could speak three words. His anterior fontanelle was still open, measuring $2\times2$ cm, lax skin was prominent, and he had a genu valgum and pes planus.

**CASE 2 (PEDIGREE A, FIG 1)**
The sister of case 1 was also born at 34 weeks' gestation; birth weight was 2.18 kg (3rd to 10th centile), length 48 cm (>90th centile), and head circumference 30 cm (3rd to 10th centile). At birth she was noted to have lax skin and dysmorphic features similar to her brother (fig 3). By one year of age her length, weight, and head circumference had fallen below the 3rd centile. Her anterior fontanelle was still widely open, measuring $6\times5$ cm, and her motor milestones were delayed. At 15 months she was unable to sit unsupported. Like her brother she had poor muscle bulk, pes planus, ligamentous laxity, and loose, redundant skin especially over her abdomen, thighs, and labia (fig 3). She also had a similar facial appearance (fig 2) with lax skin, telecanthus, a prominent nose, and downward slanting palpebral fissures. Cerebral and renal ultrasound and radiographical examination of the pelvis and hips revealed no abnormality. Other investigations which gave normal results included an electrocardiogram, serum creatine kinase, urinary organic acid screen, and prometaphase chromosome analysis.

**CASE 3 (PEDIGREE B, FIG 1)**
This boy was the first child of second cousin parents from Iraq. The pregnancy was complicated by vomiting and hypertension. He was born around term as a breech delivery. At birth he was noted to have lax skin, rubbery skin, a very soft skull with a large anterior fontanelle, and a cleft lip.

His psychomotor development has been slow. He sat alone at nine months, crawled at 13 months, and walked at two years. At four and a half years his speech consisted of single words. He began to suffer from grand mal convulsions at three years of age and was having three to four attacks a day before treatment.

At four and a half years his height was on the 50th

---

**FIG 2** Photograph showing cases 1 and 2. Note the facial appearance with lax skin and increased skin folds around the knees.

**FIG 3** Case 2 showing excessive skin folds and loose skin over abdomen, thighs, and labia in the neonatal period.
centile (107 cm) and his head circumference below the 3rd centile (47.5 cm). The anterior fontanelle was still open and measured 8×4 cm. His skin was loose especially over the face and abdomen. There were prominent epicanthic folds with hypertelorism, downward slanting palpebral fissures, and a down turned mouth (fig 4). The surgery on the cleft lip had been disrupted by an injury during an epileptic fit and had failed to repair adequately. There was no evidence of abnormal skin healing elsewhere. His finger nails were brittle and dystrophic. His primary dentition was incomplete and the teeth were carious and discoloured (fig 5).

**CASE 4 (PEDIGREE B, FIG 1)**
This girl is the sister of case 3. She was seen at five days of age and was noted to have excessive, loose skin and large fontanelles. She had a ‘clicky’ left hip. Shortly after birth the family returned to Iraq and have been lost to follow up. Details of the psychomotor development are not known.

**CASE 5 (PEDIGREE C, FIG 1)**
This girl was the second child of healthy, unrelated West Indian parents. She was born after an uncomplicated pregnancy at 35 weeks’ gestation with a birth weight of 3.54 kg. There was no perinatal asphyxia. At birth she was noted to have wrinkled skin, a prominent tongue, a short neck, and a protruding abdomen with hepatosplenomegaly and an umbilical hernia. Feeding was difficult in the neonatal period and she developed right lower lobe aspiration pneumonia. She has continued to have difficulty in swallowing with choking and a persistent cough. Her psychomotor development has been delayed.

On examination at two years, her height and weight were well below the 3rd centile (62.5 cm and 6.75 kg). However, her head circumference was on the 25th centile (47 cm). Her anterior fontanelle was still widely open. She had loose skin especially over the hands and feet. The facial skin, including the buccal folds, tended to sag. The skin over the palms and soles had an unusual velvety feel due to prominent dermal ridges. The liver was moderately

---

**FIG 4** *Facial features seen in case 3. The cleft lip was repaired but was traumatised postoperatively leading to a poor cosmetic result. Note the facial appearance associated with lax skin.*

**FIG 5** *Dental caries and hypodontia in case 3.*
enlarged but the spleen was no longer palpable. Fundal examination was normal. Palatal movement was reduced and she had difficulty in swallowing saliva. The motor tone was increased and the tendon reflexes brisk.

Investigations, including thyroid function tests, plasma amino acids, lysosomal storage enzymes, a mucopolysaccharide screen, and chromosomes, were normal. Radiological investigation showed marked osteoporosis with delayed bone age. There were no joint dislocations. The CT brain scan was normal. An ultrasound scan of the abdomen showed no abnormalities other than mild hepatomegaly. The visual evoked potentials and brain stem auditory evoked potentials showed a reduction in amplitude consistent with impaired central function. The swallowing difficulties were investigated by barium studies and microlaryngoscopy. No anatomical abnormality was seen and it appeared she had a central dysfunction in initiating the swallowing process.

**CASE 6 (PEDIGREE D, FIG 1)**
This boy was the first child of Bangladeshi parents. His parents were not known to be related but both came from the same rural village. He was born at 38 weeks' gestation with a birth weight of 2.1 kg. He was noted to have a short neck, epicantlic folds, an umbilical hernia, and loose skin especially over the dorsum of the hands, buccal folds, and neck. There were no neonatal problems, but in the first seven months he has had recurrent chest infections which required admission to hospital on four occasions.

His height and weight at seven months were well below the 3rd centile (59.8 cm and 5.6 kg) and his head circumference was on the 3rd centile (41.5 cm). He was initially hypotonic and had poor head control. At seven months of age he was able to sit with support.

Investigations showed normal thyroid function, TORCH screen, α1 antitrypsin, mucopolysaccharide, and lysosomal enzyme screen, immunoglobulins, and chromosome karyotype. A barium swallow and sweat test were also normal. The skeletal survey showed a generalised osteoporosis with a kyphosis in the dorsolumbar region.

**CASE 7 (PEDIGREE E, FIG 1)**
This female infant was the third child of non-consanguineous Caucasian parents from South Wales. The pregnancy was normal, delivery at 39 weeks' gestation was uneventful, and the birth weight was 3.95 kg. At birth, dysmorphic facies, lax skin, and bilateral talipes equinovarus were recorded. The karyotype was 46,XX.

Throughout the first two and a half years of life the child failed to thrive. Developmental delay was obvious at six months of age. The talipes in the right foot responded to serial plaster splints but the left required surgical correction.

On examination at two and a half years her weight was below the 3rd centile (8.2 kg). The anterior fontanelle was open. The face was asymmetrical and there was bilateral ptosis. The nasal bridge was depressed and the nose upturned. The philtrum was long and the lips thin, and the ears were low set and protruberant. Mild pectus excavatum and sloping shoulders were noted. The hands appeared large and covered with loose fitting skin which formed folds at the wrist, knuckles, and interphalangeal creases. Folds of skin were also observed in the axillary and hip creases. Muscle tone was normal but range of movement in all joints was greatly increased. The hair was sparse and wiry. The teeth were widely spaced, peg-like, and hypocalcified. The incisors and canines were carious with extensive erosion of the crowns, and there was delayed eruption of the molars and premolars. The intellectual development was compatible with an 18 month old infant.

A glucose tolerance test showed a flat response curve. The bone age was delayed. The following investigations were normal: urine and plasma amino acids, urea, electrolytes, liver function tests, capillary gases, haemoglobin and white cell count, urine mucopolysaccharide screen, cranial ultrasound, and serum virology.

**Discussion**

Cutis laxa is characterised clinically by redundant, loose skin that distorts the facial features and hangs in folds. Histological studies have shown that there is fragmentation of the elastin fibres, while collagen fibres and anchoring fibrils in the skin are normal. Unlike Ehlers-Danlos syndrome, the skin in cutis laxa, although loose, is not hyperextensible.

Congenital cutis laxa is a heterogeneous condition (table). Autosomal dominant cutis laxa usually presents in adult life but may be present from birth. It is not associated with other abnormalities and life span is normal. An autosomal recessive form of

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Classification of congenital cutis laxa.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Reference</strong></td>
</tr>
<tr>
<td>Cutis laxa (AD)</td>
<td>7</td>
</tr>
<tr>
<td>Cutis laxa and emphysema</td>
<td>17</td>
</tr>
<tr>
<td>Cutis laxa and growth/mental retardation</td>
<td>1-4</td>
</tr>
<tr>
<td>Cutis laxa, mental retardation, and corneal clouding</td>
<td>8</td>
</tr>
<tr>
<td>Cutis laxa and skeletal and genital abnormalities</td>
<td>9</td>
</tr>
<tr>
<td>Cutis laxa and osteoporosis</td>
<td>10</td>
</tr>
</tbody>
</table>
cutis laxa associated with emphysema and death in childhood has been clearly described. It does not differ cutaneously from other forms of cutis laxa, but in addition to emphysema it is associated with diaphragmatic hernia and diverticulae of the urinary and gastrointestinal tract. Congenital cutis laxa has also been reported by De Barsey et al\(^8\) with dementia, growth retardation, and corneal clouding. A ‘pseudoathetoid’ movement disorder with onset in the second year of life appears to be a striking feature in this form of congenital cutis laxa.

Another single case report by Kaye et al\(^9\) describes cutis laxa in a male infant with digital abnormalities and hypospadias. The types of congenital cutis laxa most relevant to this report are the cutis laxa associated with physical and mental retardation\(^1\text{-}^4\) and that associated with osteoporosis.\(^10\)

All the patients in this report had loose skin at birth. This has been associated with a characteristic facial appearance of downward slanting palpebral fissures, broad, flat nasal bridge, anteverted nostrils, sagging cheeks, and large ears. It has been suggested that the shape of the nose is normal in acquired cutis laxa.\(^11\) Mild developmental delay has been found in all patients, except cases 4 and 6 where follow up from the neonatal period was not possible. The tendency for improved performance to develop with age has been reported,\(^12\) but we have not had sufficient follow up to confirm this observation. Prenatal growth retardation was present in cases 2 and 6, while postnatal growth retardation was found in cases 1, 2, 5, 6, and 7. In cases 3 and 4 the physical growth was normal during the period of follow up. In case 5 the growth of the head circumference was not as severely affected as linear growth.

One feature which has not been reported with cutis laxa and retardation of growth and development is the presence of osteoporosis. This feature in association with cutis laxa has been previously described as a separate entity.\(^10\) In cases 5 and 6 there was generalised osteoporosis with delayed bone age in one and a thoracolumbar kyphosis in the other. In case 5 there was considerable psychomotor delay, while in case 6 the patient’s psychomotor development is still uncertain. On the basis of this overlap we would suggest that cutis laxa with osteoporosis may be the same entity as cutis laxa with growth and developmental delay.

Another feature which appears to be an associated abnormality in this form of cutis laxa is dental caries. In cases 3 and 7 there was widespread caries with erosion of the dental crowns. The teeth were small, widely spaced, and hypocalcified. This feature has not been reported previously in cutis laxa.

The entity of cutis laxa with retardation of growth and development has been suggested to be an X linked dominant defect, as 13 out of the 14 cases reported previously have been female.\(^13\) However, the presence of two brother-sister sib pairs in this report suggests that it is more likely to be autosomal recessive. In one of the sib pairs the parents were second cousins from the Middle East.

Following the subclassification of Ehlers-Danlos syndrome, molecular abnormalities in collagen biosynthesis have been defined. A similar understanding of the heterogeneity of cutis laxa may reveal insights into the biology of elastin. The histology of cutis laxa has shown fragmentation of elastin fibres similar to that which is seen with ageing or solar radiation. This has suggested that cutis laxa represents an abnormality in biosynthesis. However, one form of cutis laxa, which is X linked and presents in childhood, has been shown to be associated with a decreased lysyl oxidase activity and a reduction in the cross linkage of collagen and elastin fibres during biosynthesis.\(^14\) It is possible that some genetic variants of congenital cutis laxa are the result of abnormalities in biosynthesis of elastin, either at the level of the gene or in its post-transcriptional control. It might now be possible to study this, as a gene for elastin has been isolated\(^13\) and provisionally localised to the q31→qter region of chromosome 2.\(^14\)

We would like to thank Dr Leonard and Professor Brooke for referring case 5, Dr Savage for referring case 6, and Dr C Weaver for referring case 7. We would also like to thank Mrs Melanie Barham for secretarial assistance.

References

Congenital cutis laxa with retardation of growth and development


Correspondence and requests for reprints to Dr M A Patton, Department of Clinical Genetics, St George’s Hospital Medical School, Blackshaw Road, London SW17 0QT.
Congenital cutis laxa with retardation of growth and development.

M A Patton, J Tolmie, P Ruthnum, S Bamforth, M Baraitser and M Pembrey

doi: 10.1136/jmg.24.9.556

Updated information and services can be found at:
http://jmg.bmj.com/content/24/9/556

**Email alerting service**

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/