Hypertrichosis, hyperkeratosis, abnormal corpus callosum, mental retardation and dysmorphic features in three unrelated females

Minna H. Pöyhönen[a], Maarit M. Peippo[a], Leena K. Valanne[b], Kirsti E. Kuokkanen[c], Susanna M. Koskela[d], Oliver Bartsch[e], Sasan Rasi[e], Glenis J. Wiebe[f], Marketta Kähkönen[d] and Helena A. Kääriäinen[a,g]

We report three unrelated patients with hypertrichosis, mild to moderate mental retardation, and dysmorphic facial features including low anterior hairline, thick arched eyebrows, nose with broad tip and columella below alae nasi, short philtrum, thick drooping lower lip and simple posteriorly rotated ears. They also had rough skin with hyperkeratotic plaques. Feet and finger tips were broad. All of them had personality problems like aggressiveness, stubborn temperament or tendency to withdraw. Brain MRI showed thick and short corpus callosum. We believe that these patients represent a new syndrome of unknown aetiology. *Clin Dysmorphol* **13:85–90 © 2004 Lippincott Williams & Wilkins.**

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[a]Department of Medical Genetics, The Family Federation of Finland; Helsinki, Finland, [b]Department of Radiology, Helsinki University Hospital, Helsinki, Finland, [c]Department of Dermatology, Tampere University Hospital, Tampere, Finland, [d]Department of Clinical Genetics, Tampere University Hospital, Tampere, Finland, [e]Institute of Clinical Genetics, Dresden University of Technology, Dresden, Germany, [f]Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany and [g]Department of Medical Genetics, University of Turku and Clinical Genetics Unit, Turku University Hospital, Turku, Finland.

Correspondence and requests for reprints to Minna H. Pöyhönen, Department of Medical Genetics, The Family Federation of Finland, PO Box 849, FIN-00101 Helsinki, Finland.
Tel: +358 9 616 22213; fax: +358 9 645 018;
e-mail: minna.poyhonen@vaestoliitto.fi

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Introduction

We report three unrelated Finnish females with hypertrichosis, mild to moderate mental retardation, hyperkeratotic skin plaques, anomalous corpus callosum and similar dysmorphic facial features. This combination of features has not been reported previously.

Case reports

Patient 1

Patient 1 (see Figure 1) was born as the first child of healthy, non-consanguineous parents at 39 weeks gestation by caesarean section due to breech presentation. The younger maternal half-sibling is healthy and one miscarriage has occurred. Birthweight was 2880 g, length 46 cm, and head circumference 34.5 cm. In addition to respiratory problems, dysmorphic features and an abnormally low and hoarse cry were noted already at birth. The chromosomes (400 bands) and metabolic screening tests from urinary amino acids were normal. Her developmental milestones were slightly delayed. She walked independently at the age of 1 year 8 months and spoke words at the age of 2 years. At 5 years she revealed developmental delay, borderline intelligence and problems in fine motor coordination. She started normal school a year older than usual and was transferred to a special school later on. Hypertrichosis and signs at pubertal development were first noticed at the age of 8 years. Age of menarche was 10 years. At the endocrinological evaluation, gonadotrophins, prolactin, human chorionic gonadotrophin (hCG)-β, androgens, thyroid hormones, ultrasound of the abdomen and adrenal gland were all normal.

At 16 years of age she was a mildly mentally retarded female and the parents reported personality problems like aggressiveness, stubborn temperament and tendency to withdraw. Her final height was 154 cm (target height 166 cm), body mass index (BMI) 20.9 and head circumference 54.5 cm. Her facial features were distinct with a low anterior hairline, thick coarse hair with low-set posterior hairline, thick arched eyebrows with medial flare, a broad nose tip, a short philtrum, a large mouth, fleshy lips with lower lip droop and low-set posteriorly rotated ears. Ophthalmological examination was normal except for convergent strabismus and mild myopia (–2 D) of the right eye and mild hyperopia (+1 D) of the left. She had broad fingertips with prominent pads. Her big toes and feet were broad and the nails were small. Her skin was rough and she had marked hypertrichosis, especially on the back and on the upper and lower extremities. In addition, she had extensive hyperkeratotic plaques on her skin at the neck, shoulders, axillary area,

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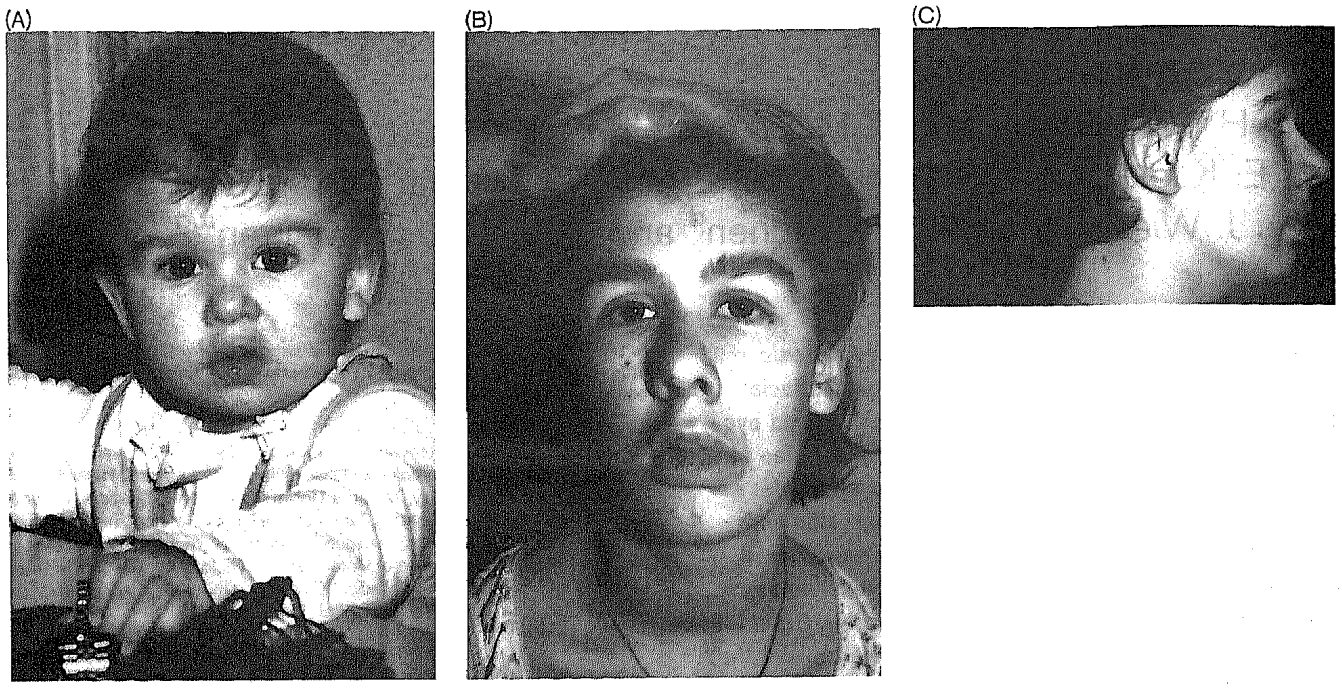
Fig. 1



Patient 1 at 2 years (A) and 16 years (B,C).

between the breasts, and on the lower abdominal and dorsal areas. Histological and electron microscopic studies of skin biopsies revealed hyperkeratosis and excluded ichthyosis. On the electroencephalogram (EEG) there was a reduction in the normal alpha activity at the occipital region and the appearance of theta rhythm became more prominent. The radiographs of the skull, spine, thorax, hands and feet were all normal. Subtelomeric fluorescent in-situ hybridization (FISH) investigations were found to be normal as well.

Patient 2

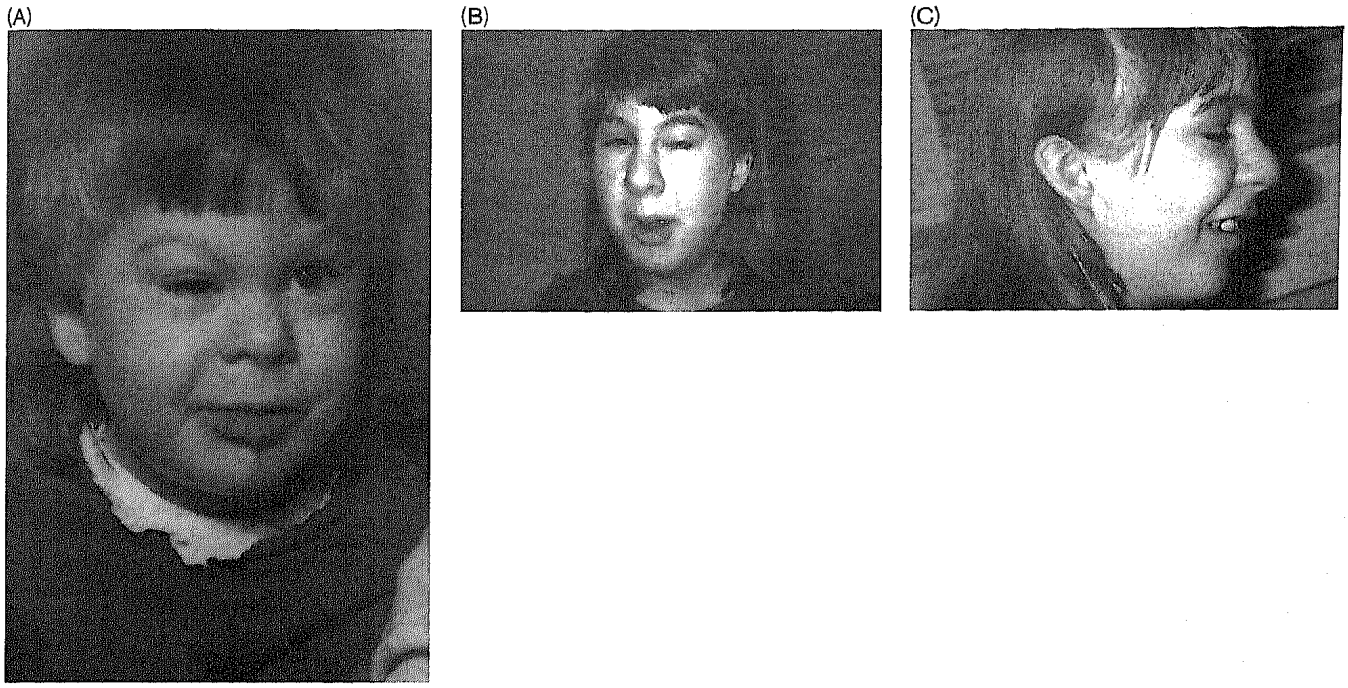
Patient 2 (see Figure 2) was born at term as the first child of healthy, non-consanguineous parents. Birthweight was 3460 g, length 48.5 cm and head circumference 34 cm. The two younger siblings are healthy and one miscarriage has occurred. She had a ventricular septal defect and patent ductus arteriosus both of which later closed spontaneously. In addition, she had a mild aortic coarctation. A congenital hip dislocation on her left was successfully treated conservatively. The chromosomes (400 bands) were studied because of dysmorphic features and were complemented later with a subtelomeric FISH study; both gave normal results. She walked at the age of 2 years 4 months and spoke words at the age of 3 years. Hypertrichosis was noted at the age of 6 years, and hyperkeratosis and multiple moles were noted at early puberty. She had moderate myopia (–4.5 D), squint and nystagmus, but optic fundi, electroretinogram (ERG) and visual evoked potential (VEP) were normal. Ptosis of the right eyelid was operated at the age of 10 years. Age of menarche was 13 years. Radiographs of the skull, thorax, spine, pelvis, hands and feet were all normal.

At 17 years of age, she was moderately mentally retarded and, according to the parents, she had a stubborn temperament and tendency to withdraw. Her final height was 154.5 cm, slightly below her target height. BMI was 25.0, and head circumference 55 cm. She had thick hair with a low-set anterior and posterior hairline, short palpebral fissures with an upward slant and ptosis on the left. The tip of the nose was broad, nares small, columella visible, philtrum short and the lower lip was thick. She also had a high and narrow palate, hyperplastic gums, broad alveolar ridges and malpositioned upper front teeth. The ears were simple, posteriorly rotated and low set. She had hypertrichosis in the upper and lower extremities and hyperkeratotic skin plaques in the middle of her back.

Patient 3

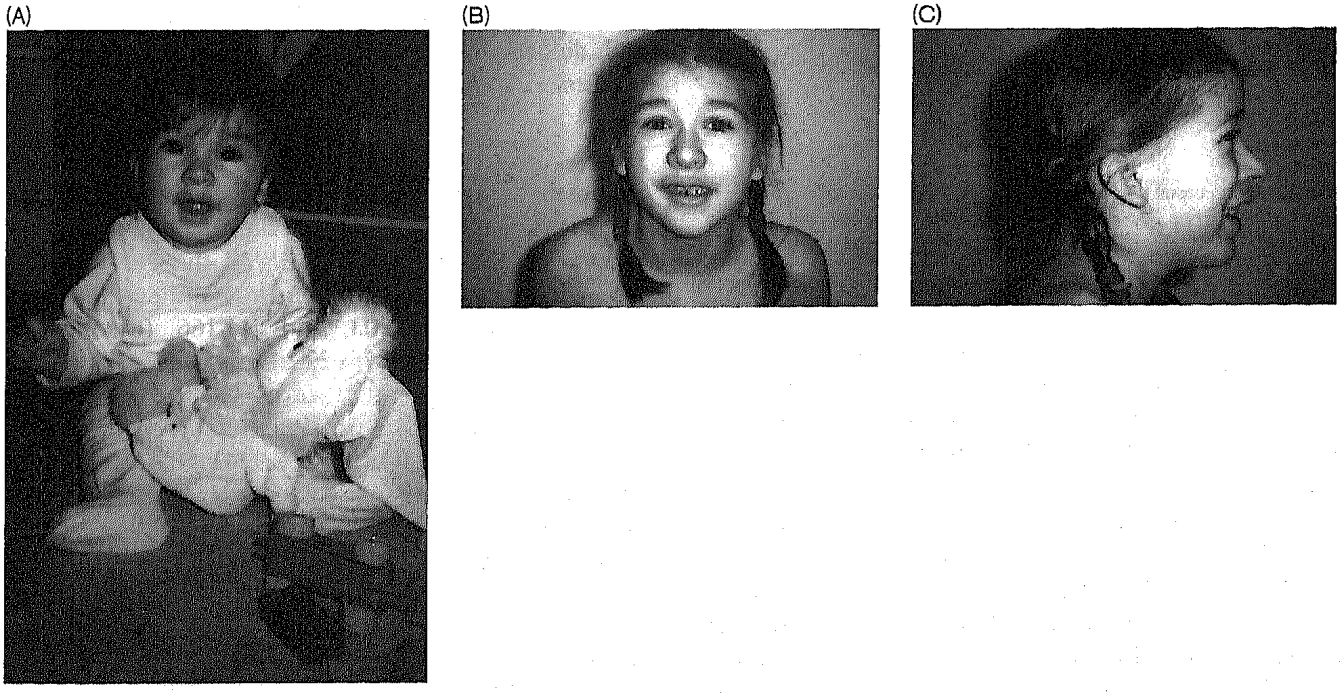
Patient 3 (see Figure 3) was born at 40 weeks of gestation after a normal pregnancy. Birthweight was 2570 g, length 46 cm, and head circumference 34 cm. She was the second child of healthy and non-consanguineous parents. The older brother and younger sister are healthy. As a newborn, she had an abnormally high-pitched cry. At the age of 2 months she was admitted to hospital because of

Fig. 2



Patient 2 at 3 years (A) and 17 years (B,C).

Fig. 3



Patient 3 at 1 year (A) and 10 years (B,C).

repeated attacks of apnoea. No specific reason was found and the attacks stopped spontaneously after 2 months. Cardiac ultrasound and radiograph of the thorax were normal. She walked at the age of 1 year 6 months and spoke sentences at 5 years of age. Her voice was high-pitched. EEG, brainstem auditory evoked potential

Table 1 Clinical features in three unrelated females with hypertrichosis, abnormally shaped corpus callosum, mental retardation and dysmorphic features

Patient number	1	2	3
Age (years)/sex	16/f	17/f	10/f
Pregnancy history			
Mild unspecific abnormalities	+	–	+
Newborn period			
Birth at term	+	+	+
Mildly small size (length <–2°SD)	+	+	+
Mild respiratory problems	+	+	+
Postnatal growth			
Head circumference normal	+	+	+
Weight normal	+	+	+
Short stature (<–1°SD or shorter)	+	+	+
Menarche (years)	10	13	–
Development and cognition			
Mental retardation	Mild	Moderate	Mild
Speaks in sentences (year)	2	3	5
Voice	Normal	Unclear	High-pitched
Ectodermal symptoms			
Hypertrichosis	+	+	+
Hyperkeratotic skin plaques	+	+	+
Rough skin	+	+	+
Dysmorphic features			
Facial features			
Low anterior hairline	+	+	+
Arched thick eyebrows with medial flare	+	+	+
Short palpebral fissures with upward slant	–	+	+
Ptosis	–	+	–
Short philtrum	+	+	+
Thick lower lip with lower lip droop	+	+	+(Slightly)
Anomalous position of upper front teeth	–	+	+
Broad alveolar ridges	–	+	+
Gingival hyperplasia	–	+	+
Small chin	–	+	+
Simple, posteriorly rotated ears	+	+	+
Low-set ears	+	+	+
Broad tip of nose, columella visible	+	+	+
Hands and feet			
Broad fingertips	+	+	+
Broad big toes	+	–	–
Broad feet	+	+	+
Small nail size	+	–	–
Brain MRI			
Thick and short corpus callosum	+	Not available	+
Chromosomes	Normal	Normal	Normal
Subtelomeric FISH	Normal	Normal	Normal

(BAEP) and VEP examinations were normal. She had mild myopia (–3 D). The chromosomes (400 bands) and subtelomeric FISH analysis were normal.

At 10 years of age her height was 132.5 cm, which was within the expected height, weight 30 kg, and head circumference 52.0 cm. She was mildly mentally retarded and the parents described her as hyperactive and stubborn. Her facial features resembled those of patients 1 and 2: low anterior hairline, thick arched eyebrows with medial flare, a short philtrum, fleshy lips, a broad nose tip and low-set ears. She also had a flat occiput, brachycephalic skull, short palpebral fissures with slight upward slant, large mouth, malpositioned upper incisors and hyperplastic gums. Her posterior hairline was low. She has had atopic eczema since early childhood and had one hypopigmented macula at the right side. The growth of body hair was increased on the forearms, back and calves. In addition, she had rough skin with hyperkeratotic plaques.

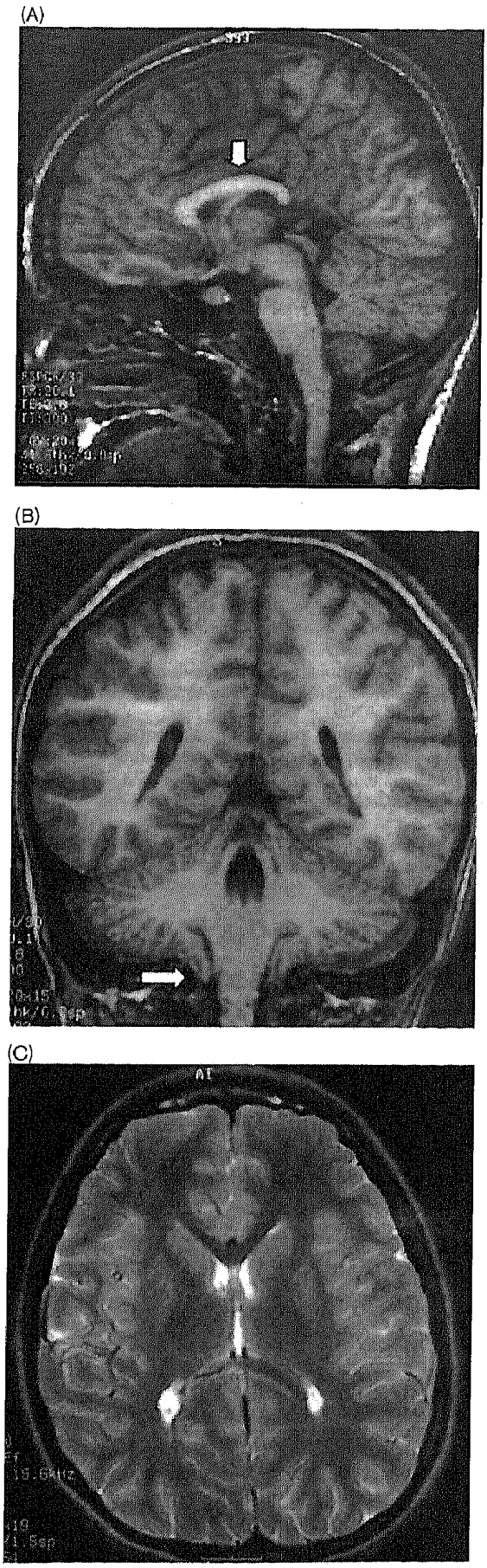
The clinical features of all three patients are summarized in Table 1. Brain magnetic resonance imaging (MRI) was done for patients 1 and 3 (see Figures 4 and 5), which revealed uniform structural abnormalities in both of them. The corpus callosum was peculiar in shape, short and rather thick with a hypoplastic splenium. Patient 3 had a typical Chiari I malformation with 11-mm downward displacement of the cerebellar tonsils towards the cervical spinal canal. Patient 1 also had beak-shaped cerebellar tonsils and mild protrusion of the cerebellar tonsils towards the foramen magnum. Otherwise the brain MRI was normal. MRI of patient 2 failed because of an anaesthetic complication. After intravenous Pentothal (thiopental) was given she developed short apnoea and laryngospasm.

Discussion

We describe three unrelated patients with hypertrichosis, mild to moderate mental retardation, hyperkeratotic skin plaques, thick and short corpus callosum, and dysmorphic facial features including low anterior hairline, thick arched eyebrows, a broad nose tip, a short philtrum, a thick drooping lower lip and simple posteriorly rotated ears. Our impression was that they all had similar features and did not resemble any of the previously reported syndromes featuring hypertrichosis.

However, as there was some facial resemblance with Rubinstein–Taybi syndrome and since one girl (patient 1) had slightly broad first toes, we did molecular cytogenetic and molecular studies of *CREBBP*, the gene for Rubinstein–Taybi syndrome. FISH, using the cosmids RT100, RT102, RT191, RT203, and RT166 (cosmids cover *CREBBP* exons e31-e17, e29-e14, e13-e3, e3, and e2-e1, respectively) that detect deletions at the *CREBBP* gene in 10% of patients with Rubinstein–Taybi syndrome (Giles *et al.*, 1997; Bartsch *et al.*, 1999), yielded normal results. The fact that no molecular cytogenetic deletions were found further supported our impression that these females did not have Rubinstein–Taybi syndrome. We also studied DNA extracted from the peripheral blood of all three patients and their close relatives using genomic sequencing with the BigDye Terminator Chemistry (Applied Biosystems, Foster City, CA, USA) and an Applied Biosystems 310 DNA sequencer (Bartsch *et al.*, 2002). From patient 1 a sequence variation in *CREBBP* exon 31, g.6624A > C, was found. The sequence variation predicts a p.Q2208H missense mutation at the protein level. As the same change was also found in the unaffected mother of patient 1, it most likely is an unrelated polymorphism. In patients 2 and 3, no

Fig. 4



sequence variations predicting changes at the protein level were detected.

Of the other syndromes featuring hypertrichosis, only Cantu syndrome and Zimmermann–Laband syndrome showed enough resemblance to require differential diagnostic consideration (Garcia-Cruz *et al.*, 2002). However, Cantu syndrome patients usually have slightly different facial features from our patients, typical changes in skeletal radiographs not present in our patients and either mild or absent mental retardation (Rosser *et al.*, 1998). Zimmermann–Laband syndrome patients have nail defects and various skeletal anomalies (Stefanova *et al.*, 2003) not present in our patients. Other hypertrichosis syndromes could be clearly distinguished because of some specific features not present in our patients, such as persistent lanugo hair (Garcia-Cruz *et al.*, 2002), acro-osteolysis (Brennan and Pauli, 2001), cutis tricolour and corpus callosum hypoplasia (Ruggieri *et al.*, 2003) and brachymetacarpalia (Göhlich-Ratmann *et al.*, 2000). Mégarbané *et al.*, (2000) reported a patient with a chromosomal abnormality. The facial features of their patient resemble those of our patients. However, our patients' chromosomes and subtelomeric FISH analyses were normal. The mentally retarded dysmorphic girl reported by Steiner and Marques (2000) also showed some facial features similar to our patients, namely, thick arched eyebrows, broad tip of nose and large mouth, but not a strikingly thick lower lip. She also lacked the hyperkeratotic skin plaques and computed tomography (CT) scan of the brain was normal.

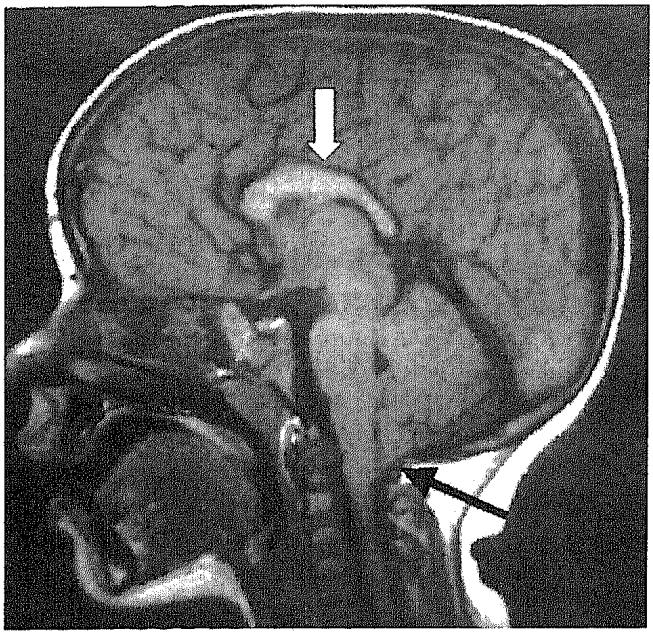
Thus, we believe that our three patients, all of Finnish origin, represent a new dysmorphic syndrome with hypertrichosis as one of its most striking features. The fact that two of our patients had a combination of callosal anomaly as well as a displacement of cerebellar tonsils further suggests that these patients represent a specific entity. Unfortunately, MRI failed in patient 2 and her possible brain anomalies are not known.

As all the three patients were sporadic cases there is no clue to the aetiology of this syndrome. These three patients had altogether four healthy siblings and one healthy half-sibling. In all the cases, the parents were unrelated and from different parts of Finland. According

Fig. 4

MRI of patient 1. (A) The corpus callosum is thick and short (arrow). A T1 weighted sagittal image. (B) The beak shaped cerebellar tonsils protrude towards the foramen magnum (arrow), a T1 weighted coronal image. (C) An axial image illustrates the short sagittal diametre of the corpus callosum and normal size of the ventricles. A T2 weighted image.

Fig. 5



MRI of patient 3. The abnormal shape of the corpus callosum is identical to patient 1 (white arrow). The cerebellar tonsils are low lying and beak shaped (black arrow). A T1 weighted sagittal image.

to our experience, the course of the disease is non-progressive, at least until early adulthood.

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