RESEARCH ARTICLE

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Long-Term Follow-Up of Four Patients With Langer–Giedion Syndrome: Clinical Course and Complications

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Long-term observations of individuals with the so-called Langer–Giedion (LGS) or tricho–rhino-phalangeal type II (TRPS2) are scarce. We report here a on follow-up of four LGS individuals, including one first described by Andres Giedion in 1969, and review the sparse publications on adults with this syndrome which comprises ectodermal dysplasia, multiple cone-shaped epiphyses prior to puberty, multiple cartilaginous exostoses, and mostly mild intellectual impairment. LGS is caused by deletion of the chromosomal segment 8q24.11–q24.13 containing among others the genes EXT1 and TRPS1. Most patients with TRPS2 are only borderline or mildly cognitively delayed, and few are of normal intelligence. Their practical skills are better than their intellectual capability, and, for this reason and because of their low self-esteem, they are often underestimated. Some patients develop seizures at variable age. Osteomas on processes of cervical vertebrae may cause pressure on cervical nerves or dissection of cerebral arteries. Joint stiffness is observed during childhood and changes later to joint laxity causing instability and proneness to trauma. Perthes disease is not rare. Almost all males become bald at or soon after puberty, and some develop (pseudo) gynecomastia. Growth hormone deficiency was found in a few patients, TSH deficiency so far only in one. Puberty and fertility are diminished, and no instance of transmission of the deletion from a non-mosaic parent to a child has been observed so far. Several affected females had vaginal atresia with consequent hydrometrocolpos.

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INTRODUCTION

Andres Giedion [1969] reported a series of individuals who had cone-shaped epiphyses and other manifestations of the tricho–rhino-phalangeal syndrome (TRPS). Among these was a 14-year-old boy who had additional findings such as multiple cartilaginous exostoses (MCE) and developmental delay. Giedion postulated that this patient has a specific syndrome distinct from TRPS. Soon thereafter, Langer [1969] and Gorlin et al. [1969] each described a patient with a similar combination of findings. Gorlin found two older reports of patients who probably had MCE and cone-shaped epiphyses [Alé and Caló, 1951; Keizer and Schilder, 1951]. Hall et al. [1974] reported these and other patients and defined the condition as being characterized by large protruding ears, bulbous nose, elongated upper lip with flat philtrum, thin and sparse scalp hair, winged scapulae, multiple cartilaginous exostoses, multiple cone-shaped epiphyses, redundant skin, and developmental disability and named the condition Langer–Giedion syndrome (LGS). In order to distinguish it from TRPS, the latter was split into TRPS1 (without exostoses and intellectual disability, OMIM 190350) while Giedion's and Langer's patients would run under the designation tricho–rhino-phalangeal syndrome type II (TRPS2; OMIM 150230). Bühler et al. [1987] described a similar patient in whom they found an interstitial deletion of 8q24.11–8q24.13 and suggested (correctly, as it turned out) that the deleted segment would include both a gene for cone-shaped epiphyses and a gene for multiple hereditary exostoses. Later it was shown that the gene main gene for multiple hereditary exostoses, exostosin-1 (*EXT1*; OMIM 133700) and the gene for TRPS1 (OMIM 190350), which encodes for a zinc finger transcription factor, both map to 8q24.11–q24.13 [Lüdecke et al., 1995].

Although more than 100 patients with TRPS2 have been reported in the literature, there is little long-term follow-up of these individuals and thus little knowledge about course and potential further complications and health risks during adulthood and advanced age. To fill this gap, we describe the course of four patients affected with TRPS2 including the original patient of Andres Giedion [1969].

CLINICAL REPORTS

Patient 1 (From Zürich)

The propositus, a male, was last seen at age 65 years. He was born in 1948 when his mother was 28 and his father 35 years old. He has one younger sister. The pedigree is inconspicuous.

During childhood he suffered from repeated upper airway and pulmonary infections, sometimes accompanied by febrile seizures. At 5 years 9 months of age (Fig. 1A–E), he presented with a height of 103 cm, a head circumference (OFC) of 47.5 cm (both <3rd centile), plagiocephaly, sparse scalp hair, asymmetric face, large and prominent low-set ears, large nose with bulbous tip, prominent lateral palatine ridges, and very carious deciduous teeth. Vision and hearing were normal. Genitalia were normal, joints were hyperextensible. Multiple cone shaped epiphyses and cartilaginous exostoses were seen on radiographs, some of the latter even on inspection as prominences, especially around shoulders, knees, and ankles. Hands showed clinodactyly of fifth fingers and a right transverse palmar crease. He had a reduced panniculus, cutis laxa, dry skin with reduced sweating, and muscular hypotonia. Radiographs showed multiple exostoses, especially on wrists, knees, ankles and ribs, and multiple cone-shaped epiphyses on metacarpals and phalanges [Giedion, 1969].

Puberty started at age 17 years and was accompanied with rapid balding. He shaved daily; axillary and pubic hair was sparse. At age 33 years (Fig. 1F) his measurements were: height 1.57 m (<3rd centile), weight 58 kg (25th centile), OFC 54 cm (15th centile, but without hair). At that age, mobility was reduced for extension and flexion of hands and feet, radial abduction of hands, and all excursions at ankles. Excursions were normal at neck and elbows. At that time, he had a funnel chest, moderate thoracolumbar scoliosis, bilateral gynecomastia or pseudo-gynecomastia, and, on radiographs, also a small skull, large maxilla and mandible, shortness of the right fifth metacarpal, distal first phalanges, and all five mesophalanges. Generally, dysmorphic facial patterns were distinctly less pronounced as compared to the previous examinations.

He was admitted to a primary school and finished with the lowest level of a normal school. Thereafter, he passed 1 year of training as a mechanic and continued working for many years as an unskilled laborer laying cables for the Swiss Railways. He could care for himself and spoke in correct sentences.

On radiographs at age 33 years the multiple exostoses were less striking than at previous examinations, some of them had even been shrinking or were integrated into the bones from which they had emerged.

At age 57 years he had a stroke which occurred during sleep when he turned his head. Examination revealed left hemiparesis including ptosis and miosis on the right side, dysarthria, and on MRI a striatocapsular infarction. Radiographs showed an osteoma on the second cervical vertebra causing dissection of the internal carotid artery. Six months later the MRI picture had improved while the neurologic deficits had not. Since then he discontinued his work for the railways. In 2010, at age 63 years, gastro-esophageal reflux was diagnosed and treated conservatively. At that time his mother, who had cared for him, died and he moved to a home for disabled elderly persons. At the last consultation in 2013 when he was 65 years old, he could again walk with help although the left upper and lower extremities were weaker than the right. He spoke again, but it was difficult to understand him. He was otherwise healthy but he complained about limited mobility due to joint restriction combined with the sequelae of the stroke. The dysmorphic pattern remained unchanged.

Patient 2 (From Zürich)

This male was born in 1958. We have no information about the early course except that he developed multiple cartilaginous exostoses

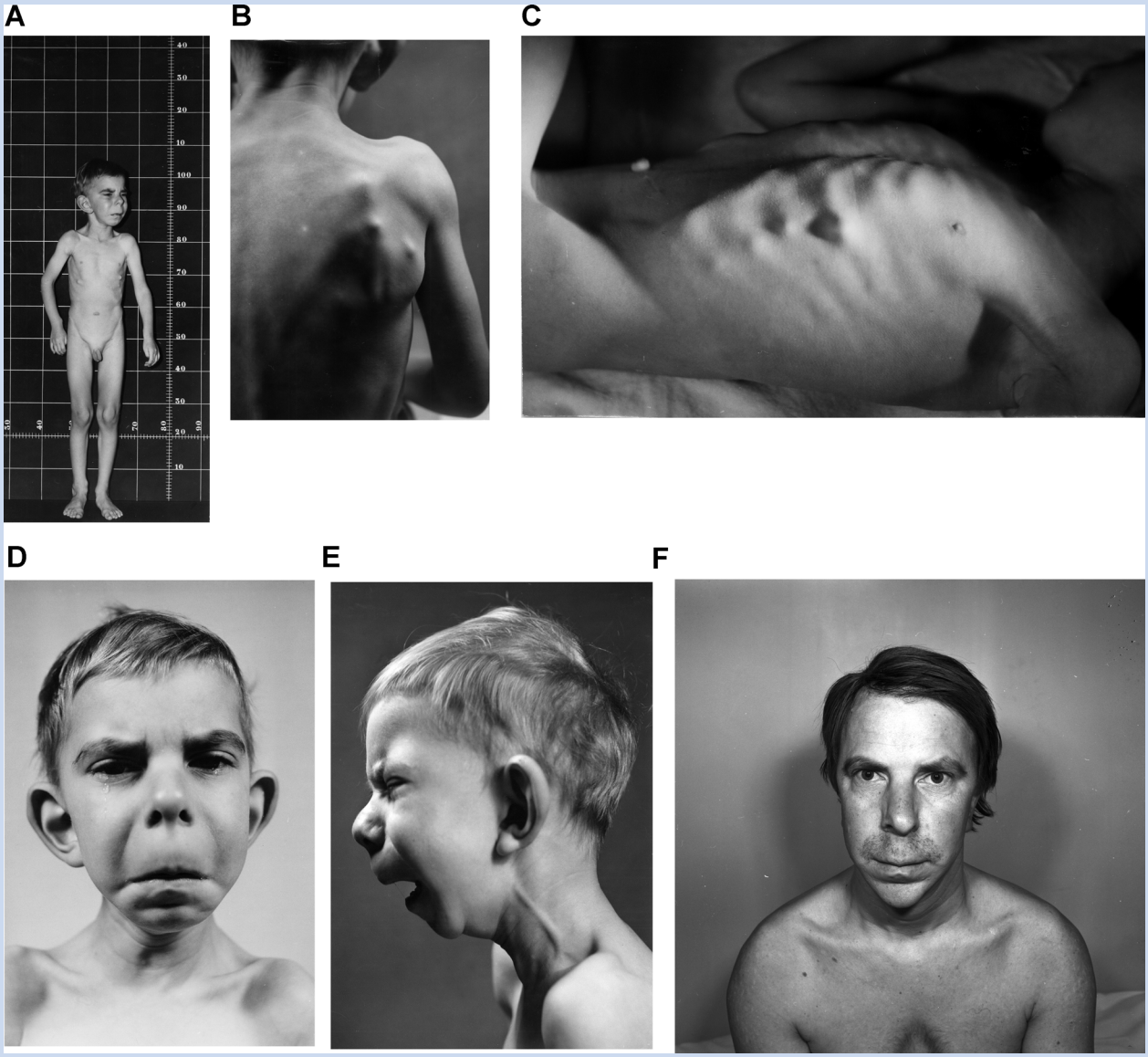

FIG. 1. A–F: Patient 1 at age 5 9/12 (A–E) and 33 (F) years of age. Note dysmorphic patterns (A–D,F), visible exostoses (B,C), and gynecomastia (F). On (F) he is wearing a wig.

and that he showed multiple cone-shaped epiphyses on metacarpals and phalanges. Scoliosis developed during childhood and became more severe during adolescence.

At age 8 years he was sent to a foster home. Puberty and balding began at about 17 years. According to records radiographs showed multiple cone-shaped epiphyses and multiple cartilaginous exostoses.

At age 22½ years he was examined clinically and cytogenetically (Fig. 2A–E). Measurements: height 1.385 m (not considering his scoliosis), weight 32 kg, OFC 49 cm without hair (all far below the 3rd centile). He had an asymmetric skull and face, small and dysmorphic ears with a right preauricular tag, a large and bulbous nose, normal teeth, a prominent mandible; funnel chest and severe right-convex thoraco-lumbar scoliosis.

Excursions were restricted, especially flexion in hips and knees and virtually all movements in ankles, wrists, and shoulders while excursions in finger and toe joints were unlimited. The left arm and leg were shorter than the right.

Radiographs showed microcephaly, a large mandible, few cartilaginous exostoses on ribs, severe thoraco-lumbar scoliosis, a grapefruit-sized exostosis over the left sacro-ileal joint, multiple exostoses on knees, ankles, and wrists leading to synostosis of ankles, short metacarpals and mesophalanges, and multiple exostoses on hands and feet.

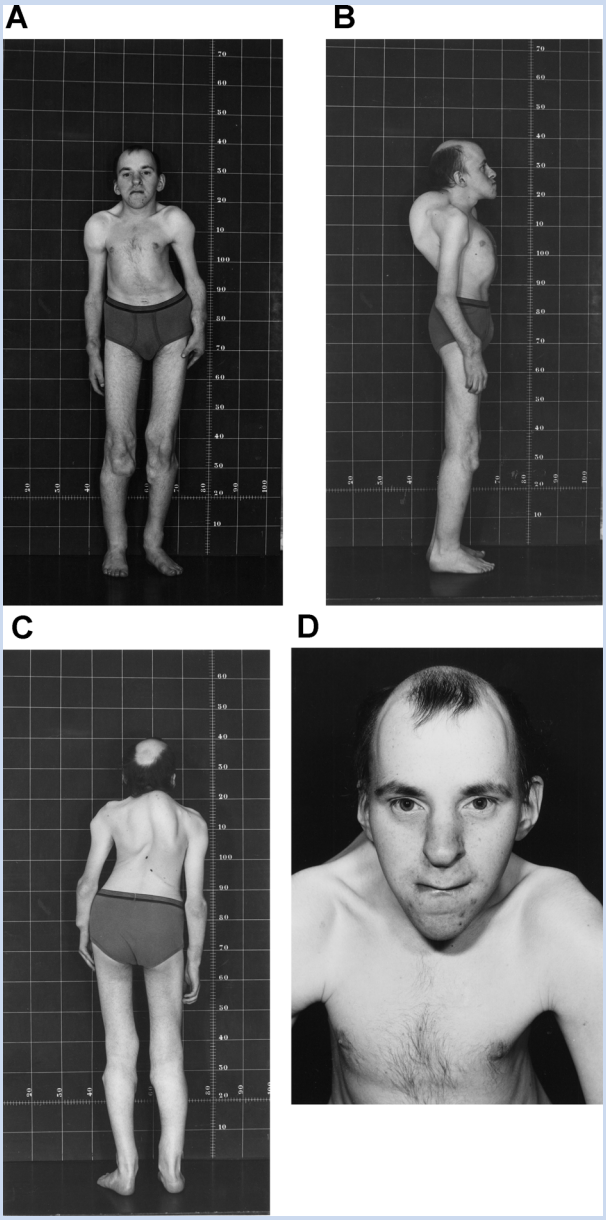

FIG. 2. A–E: Patient 2 at age 23 years. Note baldness, severe scoliosis, and visible exostoses over shoulders, elbows, knees, and ankles.

At the age of 21 and again 22 years he suffered from a myocardial infarction. At examination a systolic murmur was remarked. He was slightly cyanotic, increasing at exercise. An electrocardiogram showed right ventricular hypertrophy.

In the last years, after attending a school for persons with intellectual disabilities, he lived in an institution for those with developmental disabilities. He dressed and undressed himself, spoke with a limited vocabulary, was toilet-trained, cooked, made coffee, and cared for the kitchen.

He was lost for follow-up, and we do not know if he is still alive.

Patient 3 (From Salvador)

The patient, a boy was born in 1991. He was the third child of a healthy nonconsanguineous couple. The father was 41 and the mother 30 years old at the birth. There are no similar cases in the family. His father had worked in a petrochemical company for the last 10 years, with occupational contact with benzene and its derivatives. Delivery was in at 41 weeks. Birth weight 3,110 g (3rd centile); length 46 cm (<3rd centile), and OFC was 36 cm (75th centile). Apgar scores 9 (1′) and 10 (5′).

He held his head upright at 5 months, took his first independent steps at 1 year and 2 months and spoke his first words at 1 year and 6 months of age. He was 4 months old when referred to our community genetics program for classification of a genetic disorder. His dysmorphic pattern was consistent with LGS (Fig. 3A). On examination, he showed retarded growth and motor development; large, protruding, and low-set ears; bushy eyebrows; large and bulbous nose; naso-labial fold elongated and prominent; thin upper lip vermilion, high and narrow palate; mild micrognathia; sparse hair; thin and loose skin over the neck; multiple skeletal anomalies

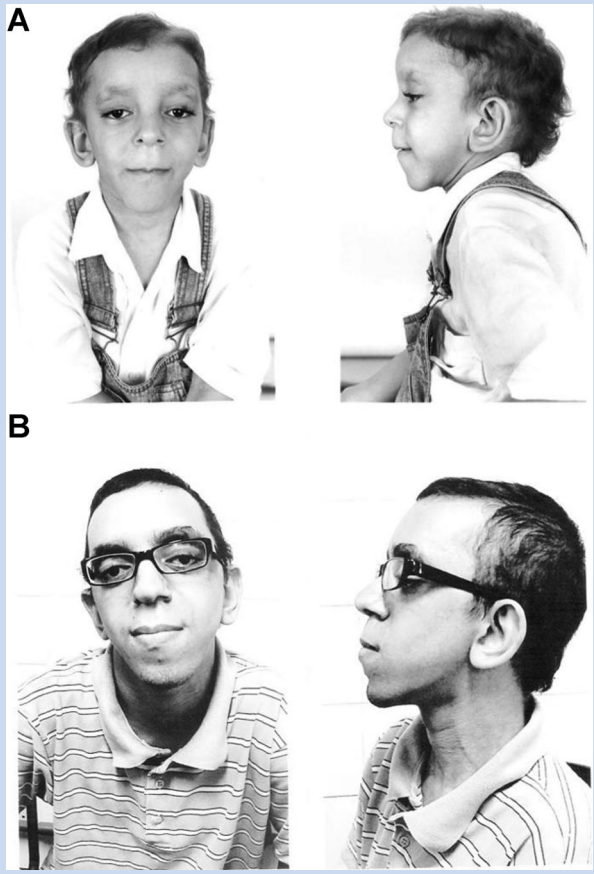

FIG. 3. A,B: Patient 3 at 6 years (A) of age. Note the dysmorphic pattern including, bulbous nose with prominent philtrum, thin upper lip, and protruding ears. B: The same patient when 20 years old with milder facial features.

(see below); repeated respiratory infections; and inguinal hernia on the right side, corrected surgically 6 days after birth together with bilateral cryptorchidism. Chronic gastritis and severe gastro-esophageal reflux were diagnosed at age 8 years.

Radiographically, at 6 years of age he showed multiple anomalies: fifth finger clinodactyly, bilaterally; crowding of toes on both feet, osteopenia; metaphyseal osteochondromas in the proximal and distal portions of long bones of upper and lower limbs; cone-shaped epiphyses of the proximal and middle phalanges; coxa valga and hip subluxation with Perthes-like changes of femoral epiphyses. He was submitted to several surgical procedures for removal of osteochondromas (forearm, right femur, knee, ankle). At age 12 years, he had surgery because of fracture of the right upper femur. From initial assessment to date, there have been periodic re-examinations.

Psychometric evaluation (Columbia Mental Maturity Scale) at age 6 years indicated normal intellectual performance. Mental age of about 6 years and 6 months was estimated, thus in the upper middle range. School performance was within the normal range.

At 17 years of age, he was diagnosed with myopia and, currently uses glasses (2.25 d for both eyes). Since the age of 15 years, vomiting improved following treatment with chlorpromazine (40 mg/day). At 18 years of age, he still had gastritis of the antrum, improving after treatment with pantoprazole (20 mg/day) and bromopride (10 mg daily). One year later a repeated endoscopy showed no abnormalities. Presently, these medications are used only occasionally when he presents with major problems of reflux.

A last re-evaluation at 20 years of age he showed a good overall development. He was active, communicative and just finished high school. His height was 156 cm (<3rd centile); weight 54 kg (10th centile); head circumference 56 cm (75th centile). His chronic joint pain and skeletal abnormalities persist, but the loose and redundant skin folds of childhood were considerably less prominent. The hyperextensible joints, manifested in childhood, were no longer observed. At age 21 years he showed thinning of the scalp hair in the parietal regions but no true baldness, and the dysmorphic facial features became milder (Fig. 3B).

Patient 4 (From Zürich)

This male was born in 1992 as the second son to a mother born 1961 and a father born 1960. The father measured 1.70 m in height, the mother 1.60 m and the older brother at 23 years 1.75 m; the latter's birthweight was 3,050 g at term. Pregnancy was uneventful, and spontaneous normal delivery took place at term. Measurements at birth: length 51 cm (10th centile), weight 3,100 g (3rd centile). At birth, absence of one right toe and syndactyly between toes 2–4 on the left were noticed. Neonatal course was normal; but a heart murmur was suspected at 6 days and a heart defect confirmed at 10 months of age. Subsequent course was marked by growth and mild developmental delay and numerous health problems. The first exostoses were noted at age 18 months. Subsequent radiographs showed, in addition, multiple cone shaped epiphyses which heightened the suspicion of TRPS2. In the following, course and different particular organ involvements, therapies. and operations are described in detail (Fig. 4A–F).

Motor development was delayed: He took his first steps at age 2 years and formed the first words only thereafter. At age 6 years he entered a special Kindergarten followed by special schooling until age 19 years. Thereafter, he trained for special work at a post office, particularly weighing and ordering of parcels and letters. He worked about 60% until recently and stayed at his parents' home. He rode the public bus and railway to and from work for about 45 min. He also could go shopping with his mother's orders. He could speak, read, and write, albeit limited. He has been a happy, peaceful, and quiet personality and very helpful at home. His concentration span has been limited. IQ was estimated at about 75. During his free time he often would ride the bicycle and performed physical exercises of various kinds. He liked television and computer games.

Two fits occurred at age 20 years. Under antiepileptic treatment he is seizure-free, and the EEG shows signs of symptomatic epilepsy including a left fronto-temporal epileptic focus. See below.

An X-ray survey at age 13 years showed about 200 cartilaginous exostoses, particular at the proximal and distal ends of femur, tibia, fibula, pelvis, phalanges, ribs, and scapulae. At age 18 years four exostoses were removed, at the distal and proximal tibia and the distal femur. In addition a Y-shaped synostosis between metatarsal 3 and 4 with absence of all phalanges of one ray was found.

A progresssive neurogenic thoraco-lumbar scoliosis necessitated operative ventral fixation (spondylothesis) of vertebrae Th11 to L3 at age 15 years. The patient wore a surgical corset for several years until shortly after operation.

An asymmetry of length of 1.5 cm with a shorter left leg was corrected by orthopaedic shoes. The latter developed after a traumatic femoral neck fracture at age 13 years.

A luxation of the left radial head was remarked at age 15 years; pronation and supination in the elbow are limited on that side. Balding set in at puberty (15 years) and resulted in total baldness by about 19 years of age. Teeth are in irregular position, and, due to narrow alveolar processes, three permanent teeth had to be extracted.

Growth hormone deficiency was diagnosed at age 9 years and treated from age 12 till growth cessation which occurred at age 16 years. At 15½ years of age his bone age was 17 years. Calculated target height would have been 1.63 m. Final height at 19 years of age was 1.465 cm with a weight of 48 kg (both below 3rd centile) and an OFC of 59.0 cm (above 97th centile despite baldness). Hand length was 14.5 cm and foot length 22 cm (both below 3rd centile).

TSH deficiency was diagnosed at age 16 years and was treated until puberty. Thereafter, TSH values improved to almost normal.

Pubertal signs were mild; he shaved 2–3 times per week and had scarce axillary and pubic hair. Voice was postpubertal. Postpubertal testosterone blood levels were normal. He showed excessive sweating.

Gynecomastia began bilaterally at age 13 years and diminished on the right side after puberty, but at age 20 years was still distinct on the left side. Testosterone treatment was without effect.

A partially anomalous pulmonary venous return (PFPVR, so-called "scimitar malformation", drainage of the left lower lung lobe

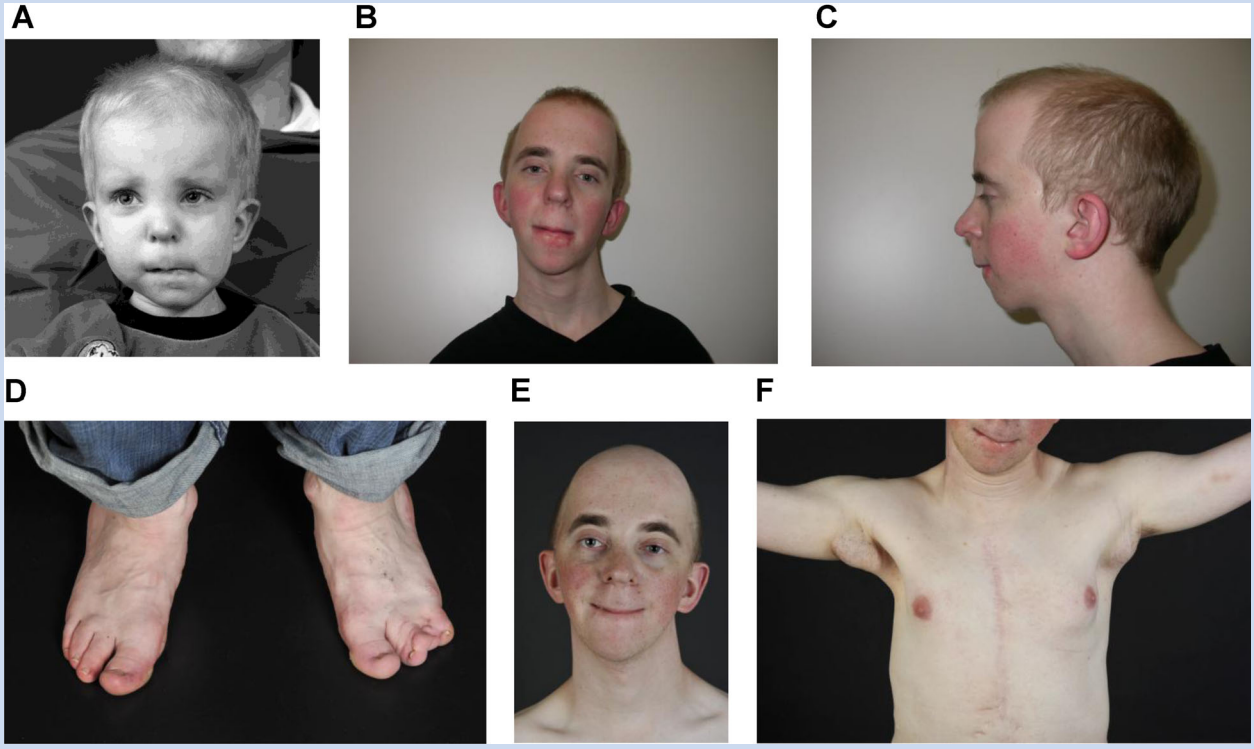

FIG. 4. A–F: Patient 4 at ages 2 ½ years (A), 14 years (B–D), and 20 years of age (E,F). Note subaxillary exostoses and left gynecomastia (F), absence of one right toe, syndactyly between left toes 2–4 (F), progressive balding and amelioration of the dysmorphic facial patterns (A–D).

into the vena cava) necessitated operative correction (the scimitar vein entered into the left atrium) at age 18 years and a re-operation 1 year later because of post-operative stenosis [Sinzig et al., 1999]. He also had an intermittent atrio-ventricular block of second grade and a bicuspid aortic valve without stenosis. A temporary diaphragmatic paresis had occurred after each of the two operations. Following two seizures, computed tomography of the brain showed a large arterio-venous malformation of the left middle cerebral artery. Magnetic resonance in addition showed a probable temoro-parietal cavernoma on the right side. Angiography was planned.

The patient has worn glasses for myopia and astigmatism since early childhood. He had several middle ear infections leading to drainage of the middle ear bilaterally at age 3 years, but apart from these episodes, his hearing was normal.

Until puberty he suffered from repeated middle ear infections and pneumonias.

CYTOGENETIC AND MOLECULAR ANALYSES

Conventional GTG banded chromosome examination revealed normal results in Patients 2 and 3 and a small interstitial deletion at 8q23/q24 in Patients 1 and 4. In Patients 1, 3, and 4, Fluorescence in situ hybridization (FISH) was performed according to the manufacturer's instructions using the locus-specific probes for the 8q23.3 region (*TRPS1*) and for the 8q24.11–8q24.12 region (*EXT1*) with a control probe for the chromosome 8 centromere (DXZ2) (Vysis, Abbott Laboratories, Abbott Park, IL). FISH analysis identified a deletion of the chromosome 8q23.3 region and of 8q24.11–8q24.12. Parental karyotypes and FISH analysis were normal. In Patients 3 and 4, the deletion was mapped through whole-genome array-CGH using a 60-mer oligonucleotide-based microarray with a theoretical resolution of 40 kb (8 × 60K, Agilent Technologies Inc., Santa Clara, CA) (Fig. 4A,B). Labeling and hybridization were performed following the protocols provided by Agilent, 2011. The arrays were analyzed through the microarray scanner (G2600D) and the Feature Extraction software (v9.5.1) (both from Agilent Technologies). Image analyses were done using Agilent Genomic Workbench Lite Edition 6.5.0.18 with the statistical algorithm ADM-2, sensitivity threshold 6.0. In Patient 3, the microarray analysis showed a single copy loss of the long arm of chromosome 8 at bands q23.3 through q24.12 which is approximately 6.43 Mb in size, including the deletion of the *EXT1* and *TRPS1* genes [arr 8q23.3q24.12(116,002,879–121,241,253)x1 (Fig. 5A,B). In Patient 4, the deletion was shorter, comprising approximately 3.7 Mb in size, but including *EXT1* and *TRPS1* as well [arr 8q23.3q24.12(116,493,571–120,223,875)x1] (Fig. 5C,D). Six genes of unknown function (NOV, ENPP2, TAF2, DSCC1, DEPDC6, and COL14A1) were present in two copies in Patient 4 but only in one copy in Patient 3. Map position is based on the

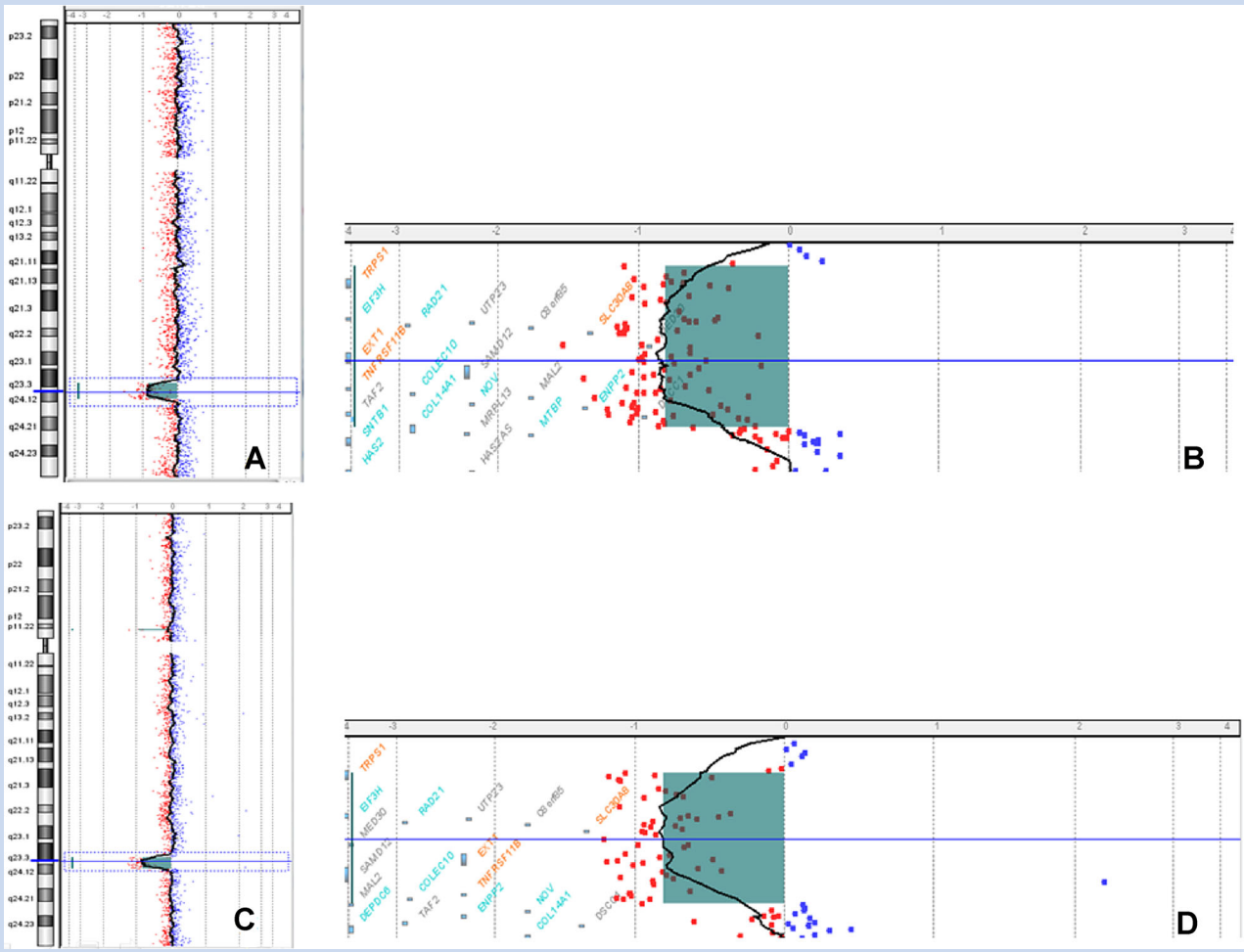

FIG. 5. Chromosome 8 array-CGH profile of the (A) Patient 3 and (C) Patient 4 (in red) and a reference DNA from a normal male (in blue). The figure shows a copy number loss corresponding to the segment of 8q23.3–q24.12 in a genomic segment with median $\log_2$ ratio shifted to −0.8. The probe $\log_2$ ratios were plotted according to genomic coordinates (based on the UCSC Genome Browser, February 2009, NCBI Build 37 reference sequence). In (B) and (D) detail of the 8q23.3–q24.12 region showing the deletion of ∼5.2 and ∼3.7 Mb segment from Patients 3 and 4, respectively.

UCSC Genome Browser, Feb. 2009, gh19 (NCBI Build GRCH37 reference sequence).

DISCUSSION

The number of distinct syndromes due to specific chromosome imbalance is rapidly increasing, especially since genomic hybridization allows detection of submicroscopic aberrations of virtually any segment. However, in contrast to this increase of information, our knowledge of the long-term outcome of most of these numerous aberrations is still surprisingly limited. Geneticists who have to inform parents that a chromosomal aberration (or any other genetic disorder) was found in their child know that one of the first questions of the couple will be about the future of their child, including survival, prognosis for mental development and schooling, health, and complications which can be expected. Often, practical questions follow that pertain to the lifetime planning for the family as well as the handicapped family member. The reason for the lack of knowledge of long-term prognosis of many chromosome aberrations is manifold: patients are mostly diagnosed (and subsequently published) during infancy and are not further followed; many publications are written by non-medical geneticists who may not have the clinical competence needed for long-term assessment of evolving clinical phenotypes; the individual aberration is very rare, often found only once in one laboratory, and thus a single case report on follow-up would not be representative, but a collaborative study is not only very time-consuming, but will also collect data of different quality. Therefore, parents of such patients are often left alone with concerns and urgent questions about the expected future of their child. The tricho–rhino-phalangeal syndrome type II (TRPS2) or Langer–Giedion syndrome (LGS) is not an exception concerning the lack of knowledge on long-term prognosis. Obligate features include cone-shaped epiphyses and multiple cartilaginous exostoses, both caused by haplo-insufficiency

of a gene with dominant transmission (*TRPS1* for the former, *EXT1* for the latter).

Most LGS patients for whom information on mental development was presented were characterized as borderline or mildly, rarely moderately mentally retarded. Even in those with mild intellectual disability or normal development, the outcome in performance was below that expected from the familial background, indicating a functional impairment that did not necessarily make them fall below the level of what is defined as normal. For example, the brother of the only mildly intellectually disabled Patient 4 of this report successfully completed a university degree. Patient 3 was reported to follow a normal intellectual development. Since his deleted segment was almost twice as large as that of Patient 4 and fully included the one deleted in the latter, there must be other genes outside the critical TRPS2 region that also influence the development in case of deletion. Patient 2 was developmentally the most delayed of the four patients. Unfortunately we could not further define his deleted segment using FISH and/or aCGH. However, his associated developmental anomalies (severe scoliosis, PFPVR) would rather indicate a larger than average deletion of the TRPS2 region. Profound cognitive disability was reported in a 22-year-old female [IQ about 10, Wilson et al., 1979]. Normal intelligence was mentioned in an 8-year-old girl by Brandt et al. [1997], a 12-year-old boy by Langer et al. [1984], a 15-year-old girl by Oorthuys and Beemer [1979] and in a patient with a larger deletion by Tiberio et al. [1999], and in an 18-year-old male by Bowen et al. [1985]. Langer et al. [1984] reviewed cases from the literature and found the development in some of them to be asynchronous, with language mostly more advanced than some motor skills and with distinct psychological problems.

Grover and Bamforth [1989] performed a detailed psychological investigation in a 13-year-old girl. Though there was mild intellectual disability in many fields, language was not delayed, self-esteem was grossly reduced, and the practical performance of their patient was considered to be distinctly higher than it could be concluded from formal IQ testing. Exactly the same pattern was mentioned by psychologists for Patient 4 of the present report. Thus it seems that patients with TRPS2 perform better in practical skills than their school achievement would suggest. The same has been observed for other chromosome aberrations, particularly for the Klinefelter syndrome [Schmid and Widmer, 1983; Schinzel, 2002]. It appears to be a common and frequent feature in chromosome aberrations with only mild to moderate mental retardation [Schinzel, 2002].

Epilepsy was occasionally reported: Bühler et al. [1983], Okuno et al. [1987], Wuyts et al. [2002], Verheij et al. [2009], and Patient 4 from this report. Patient 4 of this report has a malformation of the left cerebri media artery which became manifest through seizures at age 20 years. Since neuroradiologic investigations have very rarely performed in LGS patients, the incidence of such anomalies is unknown.

Skeletal and Orthopedic Anomalies

Mild scoliosis was reported in all four patients and in many cases from the literature, but only Patient 2 developed a severe scoliosis from childhood onward. Concerning the exostoses, the general opinion is that they do not progress further after puberty. Indeed, even radiologic controls in Patients 1 and 4 showed that the exostoses became less prominent, even shrinking, and that their connection with the underlying bone became broader with time. Apart from aesthetic disfigurement, they were, according to the patients' statements, not really harming them. There is not one instance in the literature that exostoses in a patient with TRPS2 underwent malign transformation, although Voutsinas and Wynne-Davies [1983] suggested an increased risk of malignant change (0.5% over 21 years) in patients with *EXT1* mutations. The number of reported patients with TRPS2 is far too low to draw any conclusions about their risk, however it has to be considered that deletions versus mutations of *EXT1* would not necessarily face a similar risk for malignant transformation. The most serious complication seen in one of the patients from this report was the stroke which Patient 1 had at age 57 years which was due to a growing exostosis from the second cervical vertebra. This protuberance slit the carotis interna artery causing brain infarction. A similar complication was reported in another patient with TRPS2: Miyamoto et al. [2005] reported a 23-year-old male who became tetraparetic due to an exostosis arising from the left C2 pedicle causing spinal cord compression. A 24-year-old male with *EXT1* mutation and spinal cord compression from an exostosis at T8 was reported by Quirini et al. [1996]. As almost no patients were followed up till middle age, it is possible that such events are less rare than the only two instances in the literature would suggest. Since this complication can be prevented by timely operative correction, regular radiologic examinations of the upper cervical vertebrae may be recommended from advanced adult age onward in patients with TRPS2.

Other Skeletal Abnormalities

Oligodactyly, that is absence of one or several fingers and toes, was present in Patient 4. Similar findings were rarely reported by: Pfeiffer [1980] in an 8-year-old boy, Verheij et al. [2009] in a 6-month-old girl, Stevens and Moore [1999] in a 13-month-old girl, and Fukushima et al. [1983] in a 15-year-old boy. Preaxial polydactyly was mentioned in one patient [Fukushima et al., 1983]. Tibial hemimelia with absent metatarsals was reported in a 8-year-old male [Turleau et al., 1982] and in a 13-month-old girl by Stevens and Moore [1999] and Carvalho et al. [2011] in a 4-year-old girl, lumbo-sacral agenesis in an 8-year-old girl [Turleau et al., 1982]. Further findings causing orthopedic treatment include clubfoot [Bühler et al., 1980], joint laxity with proneness to traumata, especially femoral fractures [Bauermeister and Letts, 1992, Patients 3 and 4 of this report] and Perthes disease of the hips [McGuire et al., 2000; Patient 3 of this report].

Signs of ectodermal dysplasia are mentioned in almost all patients with TRPS2. From birth onward, hair shafts are thin and brittle. Almost all male patients lose their hair almost completely at or soon after beginning of puberty. This was also the case for Patients 1, 2, and 4 of this report. However, Patient 3 seems to be an exception: at age 20 years he reportedly had more scalp hair than during childhood and adolescence, although the 8q segment deleted in him fully included the segment deleted in Patient 4 who was bald already at age 18 years. On the contrary, this patient (3) showed

less sparse hair than years before. Excessive sweating was observed in two of our patients (1 and 4). Oligodontia was reported in several patients [e.g., Pfeiffer, 1980; Patient 4 of this report], fusion of teeth in one [Schwartz et al., 1995].

Uro-Genital Anomalies

Ramos et al. [1992] described a 9-year-old female with Prune Belly malformation complex and persistent cloaca in combination with the characteristic pattern of TRPS2. Vaginal atresia and urinary reflux were reported in a 25 year-old female by Rae and Payne [1991], and hydrometrocolpos in a 3-year-old girl without exostoses (thus, probably TRPS1) by Fryns et al. [1983]. The former patient suffered from repeated abdominal pain, yet the malformation remained undiagnosed till adult age. Multipe renal cysts [Kulkarni et al., 2005] were occasionally mentioned.

Endocrine organs

Growth hormone deficiency as found in Patient 4 of this report was also described in a 10-year-old girl [Riedl et al., 2004] and thus seems to be infrequently associated to LGS. Treatment with growth hormone was effective in both patients although their growth remained restricted, presumably due to one or several genes within the deleted segment. Our patient seems to be the only one in whom so far also partial TSH deficiency was reported. Thus, it seems justified to check for growth hormone activity in patients with grossly delayed growth, considering that mild to moderate delay is common in TRSPII. A "new" finding in adults with TRPS2 is gynecomastia which developed from puberty onward in three of the four males of this report.

Cardio-vascular anomalies were reported in a minority of patients with TRPS2. Schwartz et al. [1995] reported VSD and abnormal mitral valve in a 2½-year-old male, Verheij et al. [2009] a VSD. PFPVR (the Scimitar malformation) was so far reported only in Patient 4 of this report [Sinzig et al., 1999]. In no instance from the literature were cardio-vascular malformations alone life-threatening.

Serious eye and ear anomalies are rare in TRPS2: Iridal coloboma [Pfeiffer, 1980; Verheij et al., 2009] and severe conductive hearing loss [Vantrappen et al., 1997].

In summary, the follow-up of four patients with TRPS2 to adulthood and a review of the literature show that skeletal and orthopedic problems continue to be an important issue during life; malignant transformation of an exostosis has not been observed, but two patients suffered from stroke due to a growing exostosis of an upper cervical vertebra [Miyamoto et al., 2005 and Patient 1 of this report]. Severe scoliosis and orthopedic problems due to joint laxity, the necessity for repeated operations of exostoses, Perthes disease, asymmetry of legs, joint immobility due to adjacent exostoses are among the more frequent problems in adult life. On the other hand, eye, ear, and cardiac problems are rarely of major relevance for life quality. The significance of gastro-esophageal reflux as seen in Patients 1 and 3 of this report is not clear from the literature. Intellectual disability is mild in most patients and absent in a few. Presence and importance of developmental disability does not necessarily correlate with the size of the deleted segment, as the deletion in Patient 3, who had normal intelligence, was almost twice as large and included the whole segment that was deleted in Patient 4, who had mild developmental disability. Affected individuals tend to achieve better in practical skills and to be socially underestimated because of their low self-esteem. Three of the four patients of this report and several adults from the literature could live a semi-independent life. With better knowledge on the long-term course and complications, orthopedic complications may be recognized and treated earlier and better today than what was possible in the 1960s and 70s, when individuals 1 and 2 in this study were young adults. These new data may be relevant when discussing the prognosis and providing genetic counseling about the LGS/TRPS2 to affected individuals and their family members.

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