American Journal of Medical Genetics 63:472–478 (1996)

EEC Syndrome and Genitourinary Anomalies: An Update

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We report on a large family with the ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome. The clinical manifestations in this family show great variability. Specific genitourinary anomalies were found. The propositus with micturition problems is discussed in detail. A dysplastic bladder epithelium might be the cause of these problems. A remarkable improvement of the complaints was achieved upon treatment with synthetic sulfonated glycosaminoglycans. © 1996 Wiley-Liss, Inc.

KEY WORDS: EEC syndrome, genitourinary anomalies, micturition problems, bladder epithelium, glucosaminoglycans, variability

INTRODUCTION

The ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome (MIM *129900) is an infrequent, autosomal dominant condition characterized by split hand/foot malformation, anomalies of hair, teeth, nails, nipples, nasolacrimal ducts and sweat glands, and cleft lip with or without cleft palate [Freire-Maia, 1970; Rüdiger et al., 1970; Rodini and Richieri-Costa, 1990]. Other, less frequent manifestations include developmental delay with microcephaly [Rüdiger et al., 1970; Hasegawa et al., 1991] and hearing loss [Gorlin et al., 1990]. The mutant gene causing this disorder is not known. Although most reported cases are isolated, families in which the EEC syndrome segregates as an autosomal dominant trait with incomplete penetrance [Preus and Fraser, 1973; Walker and Clodius, 1963] and variable expression have been reported [McKusick, 1994].

Received for publication January 2, 1995; revision received August 3, 1995.

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Structural anomalies of the genitourinary (GU) tract may also be part of the clinical spectrum of the EEC syndrome. Rosselli and Gulienetti [1961] were probably the first to describe structural anomalies of the GU system as an associated finding in a patient, and Preus and Fraser [1973] suggested that structural anomalies of the kidney may be an integral component of the EEC syndrome. A summary of all GU anomalies described in patients with the EEC syndrome is provided in Table I. In several texts, GU anomalies are either cited as only occasional findings in EEC syndrome [Temtamy and McKusick, 1978; Smith, 1982; Gorlin et al., 1990], or not mentioned [McKusick, 1994]. Hecht [1985] suggested to extend the acronym to EECUT syndrome, UT standing for urinary tract, to emphasize the frequent occurrence of GU anomalies. In a review of 165 case reports, Küster et al. [1986] found that 8.3% of EEC patients had associated GU anomalies. In a smaller study of 13 patients Rollnick and Hoo [1988] found that 8 patients had some GU involvement, and Nardi et al. found in a study with 25 patients 52% of the patients with GU anomalies [Nardi et al., 1992]. The exact incidence of GU anomalies in EEC syndrome remains to be determined.

Here we present a large family with the EEC syndrome in which specific GU tract abnormalities were also found. The propositus will be described in detail, the main clinical symptoms of the other relatives are summarized in Table II and shown in Fig. 1.

CLINICAL REPORT

The propositus (V-18 in Fig. 1, Fig. 2) was the sixth child of unrelated Dutch parents (mother 36, father 38 years old). He was born at term following an uncomplicated pregnancy. The lightly pigmented hair and hypoplastic nipples were noted at birth. At age 4 months he was first seen by a pediatrician because of micturition problems: his micturition required an effort and it seemed painful. Investigations showed no signs of an infection, serum creatinine level was normal (44 mmol/l) and intravenous pyelography at that time did not show any abnormalities. Because of persistence of the complaints cystography was performed at age 10 months showing no bladder abnormalities and a

TABLE I. Summary of the Literature on Genitourinary Findings in Patients With EEC Syndrome

Date	Author	Findings
1961	Rosselli and Gulienetti	Agenesis of right kidney, pelvis and ureter (case 1)
1963	Walker and Clodius	Bilateral hydronephrosis
1970	Maisels	Absent right kidney, hydronephrosis of left kidney secondary to ureteropelvic obstruction
1972	Gehler and Grosse	Left renal agenesis
1972	Brill et al.	Bilateral hydronephrosis, bladder neck contracture
1973	Swallow et al.	Hydronephrosis
1973	Kaiser-Kupfer	Congenital uni-bilateral renal agenesis
1973	Preus and Fraser	Duplication of left kidney, collecting system and ureter
1976	Bowen and Armstrong	Genital hypoplasia (case 1)
1976	Johnson	Bilateral hydronephrosis
1978	Aldenhoff et al.	Shawl scrotum; cryptorchordism; bilateral double collecting system
1978	Jamehdor et al.	Left hydronephrosis, right renal hypoplasia
1978	Schnitzler et al.	Urinary tract strictures
1978	Temtamy and McKusick	Right renal agenesis, left polycystic kidney
1980	Miner et al.	Chronic renal failure
1980	Wiedemann and Dibbern	Left renal agenesis, right hydronephrosis
1982	Duillo et al.	Right hydroureter and hydronephrosis
1982	Ivarsson et al.	Dilated renal pelvis and ureters, "prune belly"
1984	Reiffers-Mettelock et al.	Ureter stenosis, bilateral hydronephrosis
1984	da-Silva et al.	Hypospadias
1985	London et al.	Ureterocele, left hydronephrosis
1988	Rollnick and Hoo	Micropenis, ureterocele, megaureter, bladder diverticulum, hydronephrosis, renal dysplasia
1990	Rodini and Richieri-Costa	Duplication of urinary collection system, hydronephrosis, hypospadias
1992	Nardi et al.	Hypospadias, megaureter, vesicouretal reflux, ureterocele, duplication of the collecting system

slightly widened prostatic urethra. Cystoscopy showed a distal stricture of the urethra, necessitating an internal urethrotomy. However, the complaints persisted. A dilatation of the urethra was repeated several times in the following years.

At age 4 years the patient was presented to one of us (R.C.M.H.) with complaints of intermittent, burning pain in the lower abdomen lasting several hours, during which he also had a retention of urine. The micturition was forcible and difficult, and after micturition the pain disappeared completely. In periods between the attacks micturition was more or less normal. Physical examination showed no anomalies of hands or feet. There was no sweating defect and the skin was only mildly dry. Recurrent conjunctivitis was noticed.

Urodynamic studies did not show any abnormalities except for signs of anatomical obstruction. Again, a stricture of the distal urethra was seen at cystoscopy. A full thickness biopsy of the bladder wall showed a thin atrophic and dysplastic bladder epithelium without other abnormalities (Fig. 3a,b). It was concluded that the recurrent strictures of the distal urethra did not correlate well with the micturition complaints, and the abnormally thin bladder epithelium might be an explanation for the complaints. A trial with the synthetic sulfonated glycosaminoglycan "Fibrase®" (pentosanpolysulfate) was started. A remarkable improvement was achieved initially, with almost complete disappearance of all complaints. No side effects, i.e., no disturbed coagulation were detected. The similar initial improvement of complaints during treatment was noted in his sister. After a few years of treatment both children have started to complain again about episodes of minor painful sensation in the bladder.

The elder sister of the propositus (V-17 in Fig. 1, Fig. 2) had similar complaints of burning sensation in the bladder without urinary tract infection. She underwent three urethral dilatations for presumed (urodynamically not proven) urethral stenosis. At cystoscopy she had a small ulcer on the bladder dome, the rest of the picture being unremarkable. Random biopsies of the bladder demonstrated very thin atrophic bladder epithelium.

The father of the propositus (V-15), three of the five sibs (V-13 (Fig. 4b), V-16, V-17 (Fig. 6)), and nine other relatives (III-1, IV-2, IV-3, V-2, V-3, V-5, V-7 (Fig. 5a), V-10, V-12) also had manifestations of the EEC syndrome, whereas his father, a 2-year-old sister, and several other relatives had similar but less pronounced micturition complaints (Table II). In most of them these

TABLE II. Summary of Clinical Symptoms in the Present Family*

Patient	III-1	IV-2	IV-3	IV-15	V-2	V-3	V-5	V-7	V-10	V-12	V-13	V-16	V-17	V-18
Age	†	58	56	50	31	28	26	19	†	11	25	18	14	12
Sex	m	f	m	m	f	m	f	f	f	m	f	f	f	m
Ectrodactyly hand	–	u/r	u/l	–	u/l	–	–	–	–	u/r	–	–	–	–
foot	–	–	u/l	–	–	–	–	–	–	b	–	–	–	–
Syndactyly hand	?	–	–	–	–	–	–	–	?	u/l	–	–	–	–
foot	?	b	–	–	–	u/r	–	u/l	?	u/l	–	–	–	–
Other limb anomalies	?	–	–	c,d	c,d	d	–	c,e	–	c,f	–	–	c	c
Cleft lip/palate	–	–	–	–	–	–	–	+	–	–	–	–	+[b]	–
Ectodermal anomalies	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichodysplasia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dental anomalies	?	+	+	+	+	+	+	+	?	–	+	+	+	+
Onychodysplasia	?	+	+	+	+	+	+	+	?	–	+	?	–	+
Hypohidrosis	?	–	–	–	–	(+)	–	–	?[a]	–	?	?	+	+
Tear duct anomalies	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Micturition problems	(+)	–	+	+	+	+	+	+	?	+	–	–	+	+
Diminishing of micturition problems (age in years)			18	13	17	16	12	15						

* y, year; + = present; –, absent; u, unilateral; b, bilateral; r, right; l, left; (+), probably positive; c, clinodactyly of fifth fingers; d, ulnar deviation of third finger; f, abortive mesoaxial polydactyly of left hand; e, hypoplastic fifth ray of right foot.
† Deceased.
[a] Patient died at 2 years of age because of a hyperpyrexia during an infection.
[b] Indentation of upper lip.

problems diminished spontaneously around puberty although mild problems persisted. Probably hormonal changes are of significance in this respect. Other GU anomalies were not found in this family.

DISCUSSION

The EEC syndrome may be considered a heritable pleiotropic multiple congenital anomalies (MCA)/dysplasia syndrome. The most common clinical manifestations are ectodermal dysplasia, ectrodactyly, and cleft lip/palate. The clinical findings show great variations. Some relatives manifest all components of the syndrome, while others may exhibit only one or two components [Freie-Maia, 1970]. Thus, the condition is presumed to show an autosomal dominant inheritance with incomplete penetrance and variable expression [Preus and Fraser, 1973; Walker and Clodius, 1963].

The present family demonstrates well the widely variable expression of the EEC syndrome. Table II shows that the different manifestations occurred in almost every possible combination. The expression was not related to sex, age, or laterality. In fact, none of the

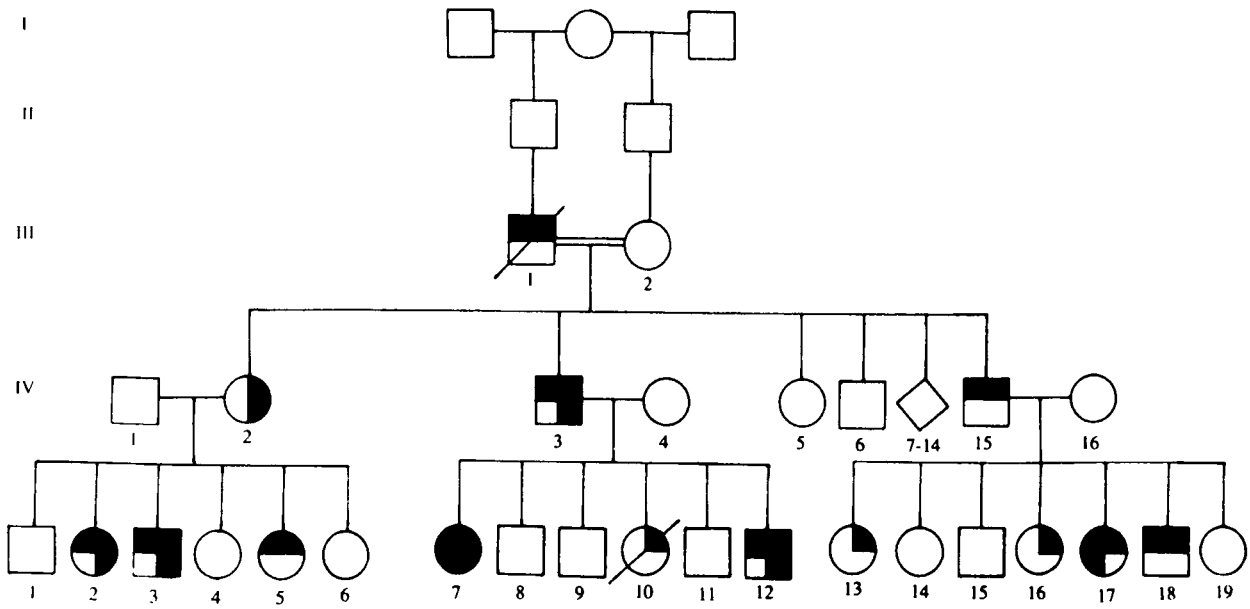

Fig. 1. Pedigree of presently described family. ◧, ectodermal dysplasia; ◩, micturition problems; ◨, schisis; ◪, ectrodactyly/limb defects.

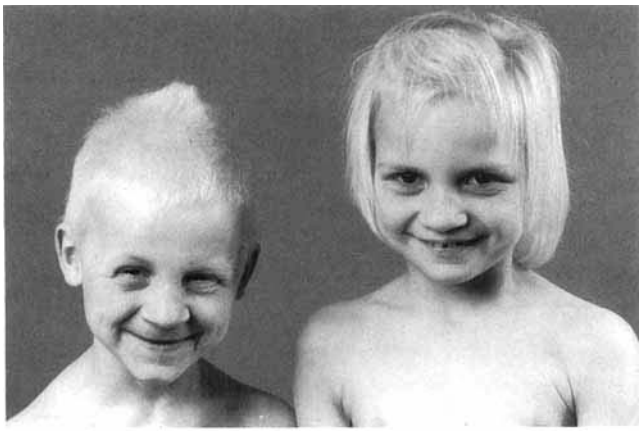

Fig. 2. The propositus (V-18) and his sister (V-17).

14 affected relatives showed the complete spectrum of the EEC syndrome, and each affected person had a different combination of signs and symptoms. This variability in expression of the syndrome is further illustrated by Figures 4, 5, and 6. It has been shown before that the phenotype of the EEC syndrome may vary considerably [Küster et al., 1985; Wallis, 1988; Rodini and Richieri-Costa, 1990]. The most constant finding is the ectodermal dysplasia, which was found in all patients recently reviewed [Rodini and Richieri-Costa, 1990]. These authors described 13 different syndromes involving ectodermal dysplasia/ectrodactyly (acral defects)/cleft lip-palate, and discussed their relationship to the EEC syndrome. It should be noted that in individual cases it may be impossible to distinguish an oligosymptomatic case with EEC syndrome from a case with such an EEC-like syndrome.

Abnormalities in the genitourinary system such as kidney and ureter malformations (duplication of the kidney, collecting system and ureter, absent kidney, small dysplastic kidney, hydronephrosis, and hydroureter) were described previously in patients with the complete or incomplete forms of EEC syndrome (Table I). Hypospadias, cryptorchidism and prune belly have been noted [Aldenhoff et al., 1978; Ivarsson et al., 1982; Nardi et al., 1992]. Obstructions on several levels of the urinary tract were described by Brill et al. [1972] and Rollnick and Hoo [1988]. In the present family (Table II) several subjects had micturition problems such as painful micturition (V-2, V-3, V-17, and V-18), or recurrent cystitis (V-2, V-7), and some had anatomical anomalies such as stricture of the distal urethra (V-17, V-18).

The propositus had the combination of mild glandular hypospadias, congenital stricture of the distal urethra, and atrophic/dysplastic bladder epithelium. Because of the poor quality of the bladder epithelium normal urine may have had an irritating effect on the bladder wall, causing the voiding problems. Normally, the surface of the bladder epithelium is lined by a layer of sulfonated glucosaminoglycans, of which the non-specific anti-adherence effect can be reproduced by synthetic sulfonated glucosaminoglycans, such as pentosan polysulfate, a heparin-like solution. The mucous layer appears to be the most important line of defense between the transitional cells at the surface of the bladder and possibly harmful substances in the urine. Many disorders associated with a deficiency in the anti-adherence activity of the glucosaminoglycan layer can benefit from treatment with synthetic glycosaminoglycans [Parsons, 1982; Parsons et al., 1983]. Pentosan-polysulfate was effective in two patients from our family.

This is the first description of atrophic/dysplastic bladder epithelium with specific micturition complaints in EEC syndrome, though we are aware of cases in the UK with similar symptoms (P.B., unreported data). Since the bladder epithelium is a tissue of mesodermal origin the pleiotropic gene causing EEC syndrome may involve other mesodermal derivatives such as the bladder epithelium, and arterial walls [Miner et al., 1980].

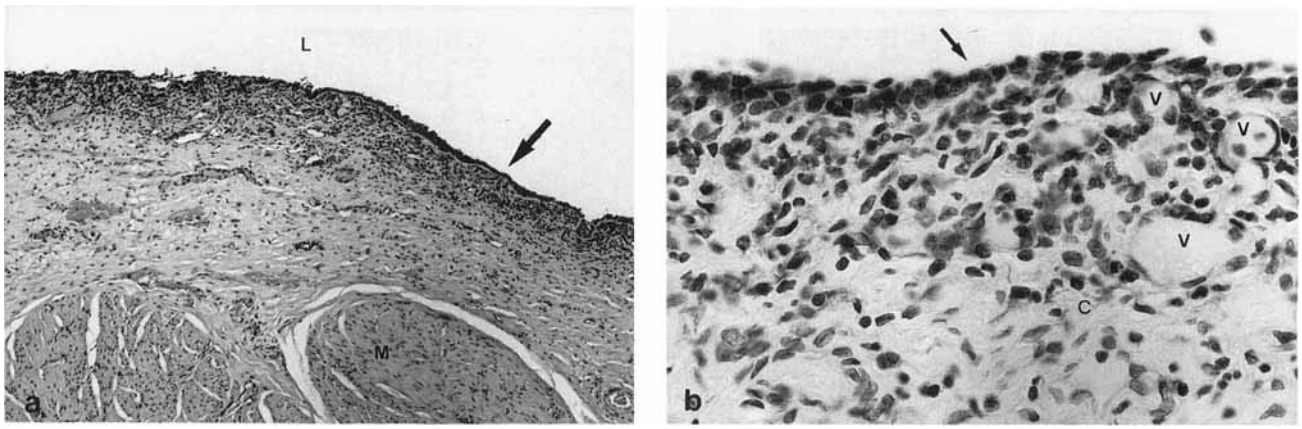

Fig. 3. Full thickness biopsy of bladder wall. **a:** General view. →, atrophic epithelium; L, lumen; M, muscle. **b:** Detail enlargement. →, atrophic epithelium; V, vessel; C, connective tissue with an increased amount of inflammatory cells (neutrophilic granulocytes, lymphocytes, plasmacells, histiocytes).

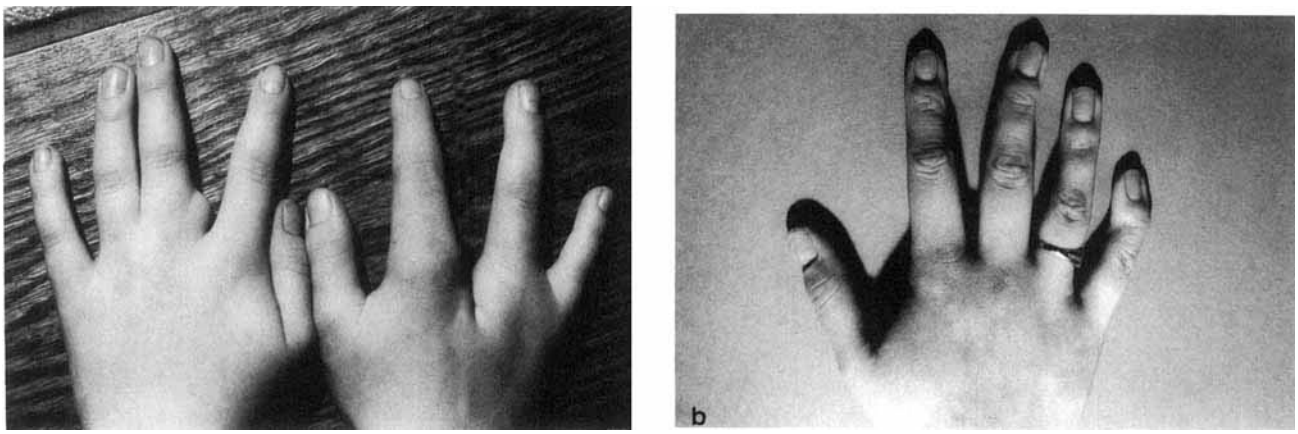

Fig. 4. Hand anomalies in the present family with EEC syndrome. **a,** V-12; **b,** V-13.

It is unclear whether the syndrome is indeed a homogeneous entity reflecting variable expression of a single mutant gene or whether multiple mutant genes result in the production of one apparent clinical entity [Jamehdor et al., 1978]. Several case reports of ectrodactyly with or without additional manifestations of the EEC syndrome associated with balanced chromosome rearrangements or interstitial deletions at 7q21–q22, suggest the existence of a locus in 7q22 for split hand/split foot differentiation [Del Porto et al., 1983; Pfeiffer, 1984; Tajara et al., 1989; Morey and Higgins, 1990; Sharland et al., 1991; Roberts et al., 1991; Rivera et al., 1991; Naritomi et al., 1993; Genuardi et al., 1993; Nunes, 1994; McElveen et al., 1995]. On the other hand, there are 17 additional deletions involving this band but not associated with ectrodactyly [Winter and Tickle, 1993]. Genetic interactions such as position effect and unmasking of heterozygosity, and extreme variability in the expression of ectrodactyly could explain this discrepancy [Lacombe et al., 1994]. Hasegawa et al. reported a reciprocal translocation between 7q11.21 and 9p12 (or 7p11.2 and 9q12) related to the syndrome [Hasegawa et al., 1991]. However, this could represent a coincidental finding, with a mutation at 7q22 cosegregating with the translocated chromosome 7. Recently, structural anomalies of chromosome 6q21 have been reported in three unrelated patients with split hand/split foot, suggesting that this region may also contain genes responsible for limb development [Braverman et al., 1993; Viljoen and Smart, 1993; Gurrieri et al., 1995].

In conclusion, the EEC syndrome is an embryonic dysplasia most likely resulting from alterations that involve epithelial/mesenchymal interactions during development. In spite of the impact of the anomalies of the face, skin, and limbs, a routine evaluation of the GU tract should be performed, since urinary complications could result in a poor prognosis for the affected patients. This is particularly important as most urinary tract problems can be detected and treated. Finally, the present report demonstrates that the EEC syndrome may be even more variable than formerly thought.

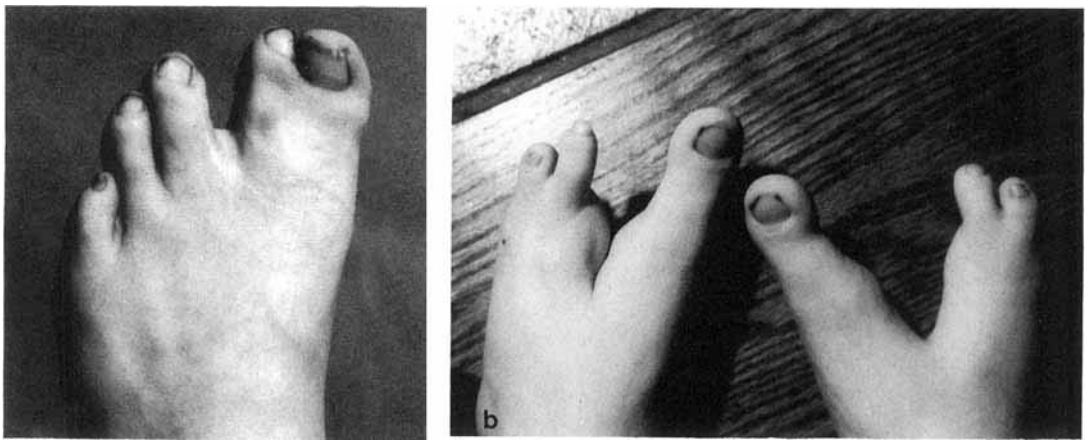

Fig. 5. Foot anomalies in the present family with EEC syndrome. **a,** V-7; **b,** V-12.

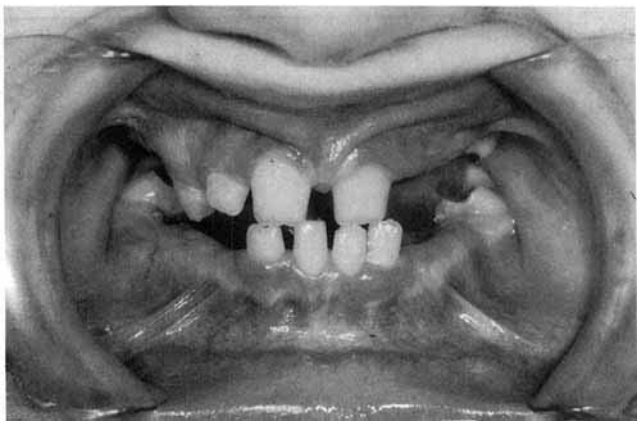

Fig. 6. Dental anomalies in the present family with EEC syndrome (V-17).

ACKNOWLEDGMENTS

We thank the present family for their cooperation during this study and Dr. W. Spliet (Utrecht) for providing Figure 3a,b.

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