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Review

The Peters' plus syndrome: a review

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Abstract

Peters' plus syndrome is an infrequently described entity that combines anomalies in the anterior chamber of the eye with other multiple congenital anomalies, and a developmental delay. Major symptoms are extremely variable anterior chamber anomalies, cupid bow of the upper lip, cleft lip and palate, short stature, broad hands and feet, and variable mental delay. The syndrome follows an autosomal recessive pattern of inheritance. The etiology is unknown, but may involve abnormal neural crest development. A review of the pertinent literature is provided.

Keywords: Peters' plus syndrome; Krause-Kivlin syndrome; Sclerocornea; Anterior chamber cleavage disorder; Mental retardation; Cleft lip and palate; Short limb dwarfism; Autosomal recessive; Neural crest; PAX6; PITX2; PITX3; FKHL7; FGFR2

1. History

The term Peters' plus syndrome was first coined in 1984 by the Dutch ophthalmologist Mary Van Schooneveld et al. [1] in describing 11 patients with developmental defects in the anterior chamber of the eye, a typical face, clefting, short limb dwarfism, and developmental delay. Kivlin et al. [2] later pointed out that Krause et al. [3] had already described a single case in 1969, and others [4,5] mentioned the 1961 report of Haney and Falls [6] with two cases. Because of the mnemonic value of the term Peters' plus, this is most commonly used in the literature. In total more than 50 cases are known ([1–21], own unpublished cases). Other reports [22,23] may have described the entity too, but lack sufficient data to be sure about the diagnosis. Inheritance is clearly autosomal recessive. Earlier reviews are available [4,5,10]. The major clinical symptoms are summarized in Table 1.

2. Clinical overview

2.1. Growth and development

Most cases have prenatal growth retardation, and virtually all cases are disproportionally short postnatally. Arms and legs are equally shortened, and although formal studies are lacking, published pictures usually show rhizomelic shortening. Adult height varies from 1.28 m to 1.51 m in females and 1.41 m and 1.55 m in males. In one pair of sibs a deficient growth hormone secretion was found, which responded well to growth hormone suppletion (Hennekam, unpublished observations).

Mental delay is present in 83% of cases, and varies from mild (34%), to moderate (20%) or severe (26%). There is no correlation between physical findings and mental development. Specific behavioral studies have not been performed, but Young et al. [21] and Hennekam et al. [4] mentioned a strikingly friendly and amiable personality in several patients; Thompson et al. [5] reported outbursts of anger and difficult behavior in another case. In two unpublished cases autism was present (Hennekam, unpublished observation).

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Table 1
Major symptoms in 49 patients with Peters' plus syndrome from literature

	Percentage
Growth and development	
Birth weight at/below third centile	87
Birth length at/below third centile	63
Postnatal height below third centile	92
Developmental delay	83
Craniofacial features	
Microcephaly	22
Macrocephaly	8
Prominent forehead	70
Hypertelorism	76
Narrow palpebral fissures	79
Upslanted palpebral fissures	32
Long philtrum	91
Cupid bow upper lip	98
Cleft lip/palate	45/33
Micrognathia	44
Small ears	42
Pre-auricular pits	37
Broad neck	73
Eyes	
Peters' anomaly	73
Any anterior chamber defect	98
Any congenital eye malformation	100
Skeletal system	
Short limbs	95
Short, broad hands	100
Clinodactyly fifth finger	91
Other findings	
Congenital heart malformations	31
Congenital renal anomalies	19

2.2. Craniofacial features

The most specific facial features are a round face in infancy, prominent forehead, hypertelorism, short palpebral fissures, long philtrum, and cupid bow's shape of the upper lip with a thin vermilion border (Fig. 1). The latter is difficult to determine in the presence of a cleft lip, but after surgical repair the typical lip configuration becomes evident. A cleft lip is present in 45% of cases, and can be accompanied by a cleft palate. Sometimes only the vermilion border is irregular, as a *forme fruste* of a cleft lip [4]. Other symptoms are small and mildly dysmorphic ears, pre-auricular pits, narrow auditory canals [2], unilateral or bilateral ptosis, mild malar hypoplasia, micrognathia, and a broad and sometimes webbed [21] neck. The lingual frenulum is frequently short. Absent [4] or abnormally pointed [5,19] lateral upper incisors, facial hirsutism [5], and prominent ears [5] have been described.

2.3. Eyes

The Peters' anomaly is characterized by central corneal opacity (leukoma), thinning of the posterior aspect of the cornea, and iridocorneal adhesions (Fig. 2) [24]. It has formerly been called anterior chamber cleavage defect, but already in 1969 Alkemade [25] explained that the anterior chamber does not arise by cleavage. Posterior embryotoxon

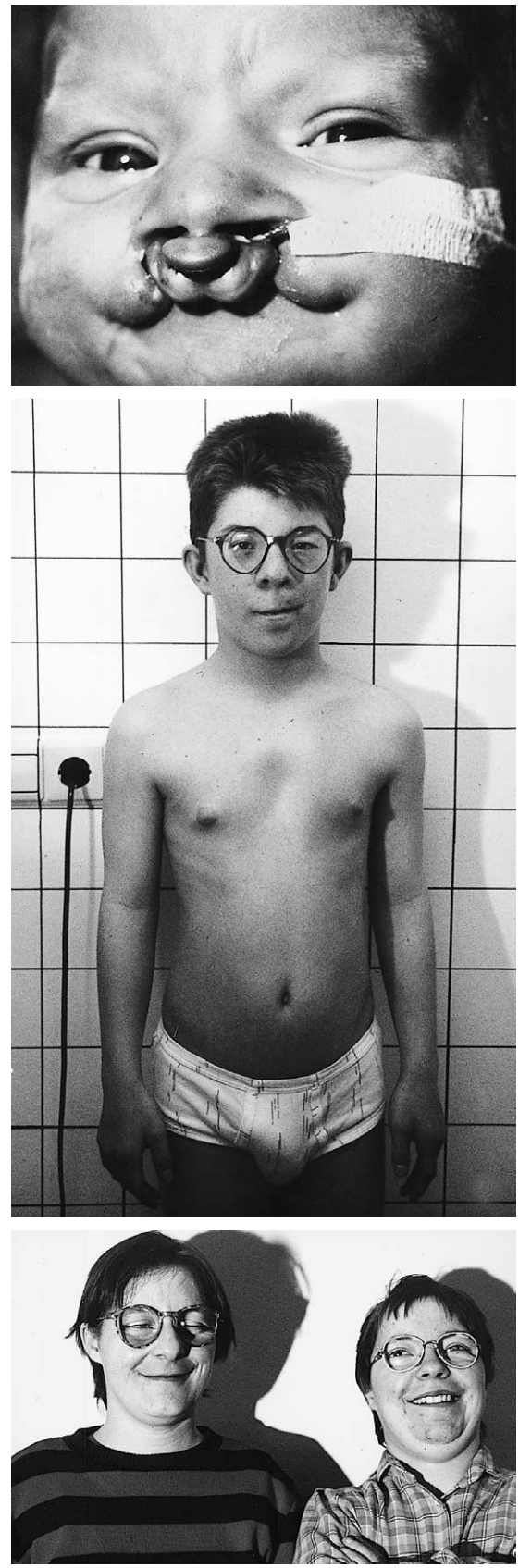

Fig. 1. Frontal view of four patients age 2 months, upper, 13 years, middle, and sisters of 42 and 31 years, lower, respectively. Note mild pectus excavatum in middle.

(also indicated as thickening of Schwalbe's line) is the least severe expression of an abnormal anterior chamber development, more severe expressions being keratoconus posterior (or keratoconus posticus circumscriptus), Axenfeld anomaly, Rieger anomaly, and iridogoniodysgenesis. In Peters' plus syndrome most commonly bilateral Peters' anomaly is found, but it can also occur unilaterally or as another form of anterior chamber defect. Some patients do not have any anterior chamber anomaly, and are only recognized because of the family history [4]. Minor anterior chamber anomalies may be easily missed in routine ophthalmologic investigations. In several cases the corneal opacities have gradually diminished in density in infancy [4,5,17,21]. Cataract and glaucoma are common complications that can also occur at a later age. Unusual eye symptoms are severe myopia [4,5], iris coloboma [2,4], retina coloboma [4,7,21], optic atrophy [7], and microphthalmia [11,18].

2.4. Skeletal system

Short limbs and brachydactyly are invariably present. The hands and feet (Fig. 3) can be very broad, which may give considerable problems in wearing shoes. No polydactyly has been reported. Clinodactyly of the fifth finger can be very marked. The elbows often show diminished mobility, the other joints can be hyperextensible. Pectus excavatum [4,6], a broad [11] or narrow [4] thorax, hyperkyphosis [4], segmentation defects of the vertebral column [21], hemivertebrae [21], scoliosis [21], and pes cavus [4,21] occur, as do mild cutaneous syndactylies [4,5,8,9,11], proximally placed thumbs [15], and deep creases in foot soles [9]. The ossification of the skull can be unusual: often the fontanel is large at birth, extending to the forehead, but within the first months rapid ossification closes the fontanels before 1 year of age [4]. No genuine craniosynostosis has been reported. Cabral de Almeida et al. [8], and Hennekam et al. [4] mentioned prominent metopic ridges, which was also present in an unpublished Dutch case (Hennekam, unpublished). Both microcephaly and macrocephaly can be present. Specific radiographic findings are uncommon but can include early arthritic changes of the upper cervical [4] or lumbar [5] spine, thoracic hemivertebrae [4], multiple vertebral segmentation defects [21], square pelvis with flat iliac crests [5], and underdevelopment of the proximal radii [15]. Hand and foot radiographs show general shortening of metacarpals, metatarsals, and (especially proximal and middle) phalanges. In one case, a regular bony defect of the proximal part of the first phalanx of the thumbs was found [14], and in another case there were cone shaped epiphyses [21].

2.5. Other findings

Hearing loss [4], recurrent cystitis [2–4,10,14,17,21], intractable diarrhea [4], fat malabsorption [15], seizures

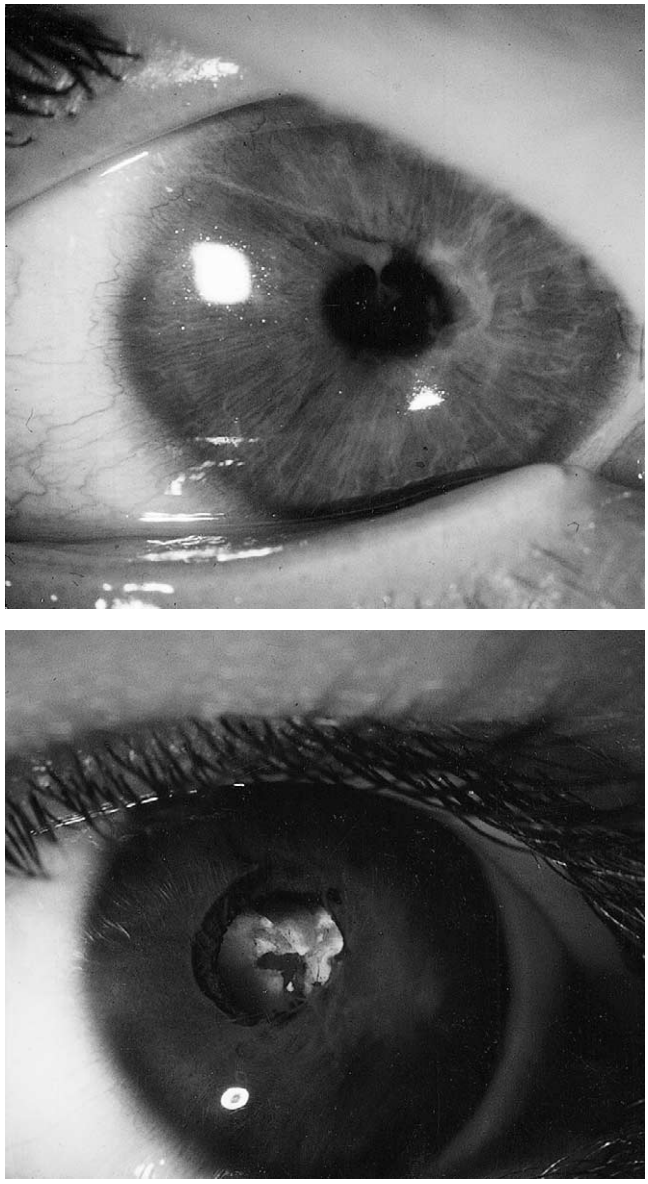

Fig. 2. Peters' anomaly. Upper. Right eye. Peters' anomaly with peripheral scleralization of the microcornea (8.0 mm), shallow anterior chamber, paracentral corneal opacities, and adhesions between anterior lens and iriskrause at 11 o'clock. Lower. Left eye. Peters' anomaly, small cornea (9.0 mm), extensive synechiae anteriores (2–5 o'clock), localized corneal opacity, iris hypoplasia, nasally displaced pupil, ectropion uveae, synechiae posteriores, and cataract.

[4,7,10], stereotypic movements [4], and high pitched voice or dysphonia [4,17] can cause physical problems. Almost all cases have feeding problems in infancy. Other reported congenital anomalies have included heart defects such as atrial septal defects [4,10], ventricular septal defects [14–16], subvalvular aortic stenosis [11], pulmonary stenosis [4,8,14], sometimes with a bicuspid pulmonary valve [14], and recurrent endocarditis [5]; genitourinary problems including hydronephosis [4,7,10,17], renal or uretral duplication [4,5,7,15,21], renal hypoplasia with oligomeganephronia [14], hypospadias [4,10], incomplete foreskin [10], cryptorchidism [2,4,10,21], hypoplastic clitoris [16], hypo-

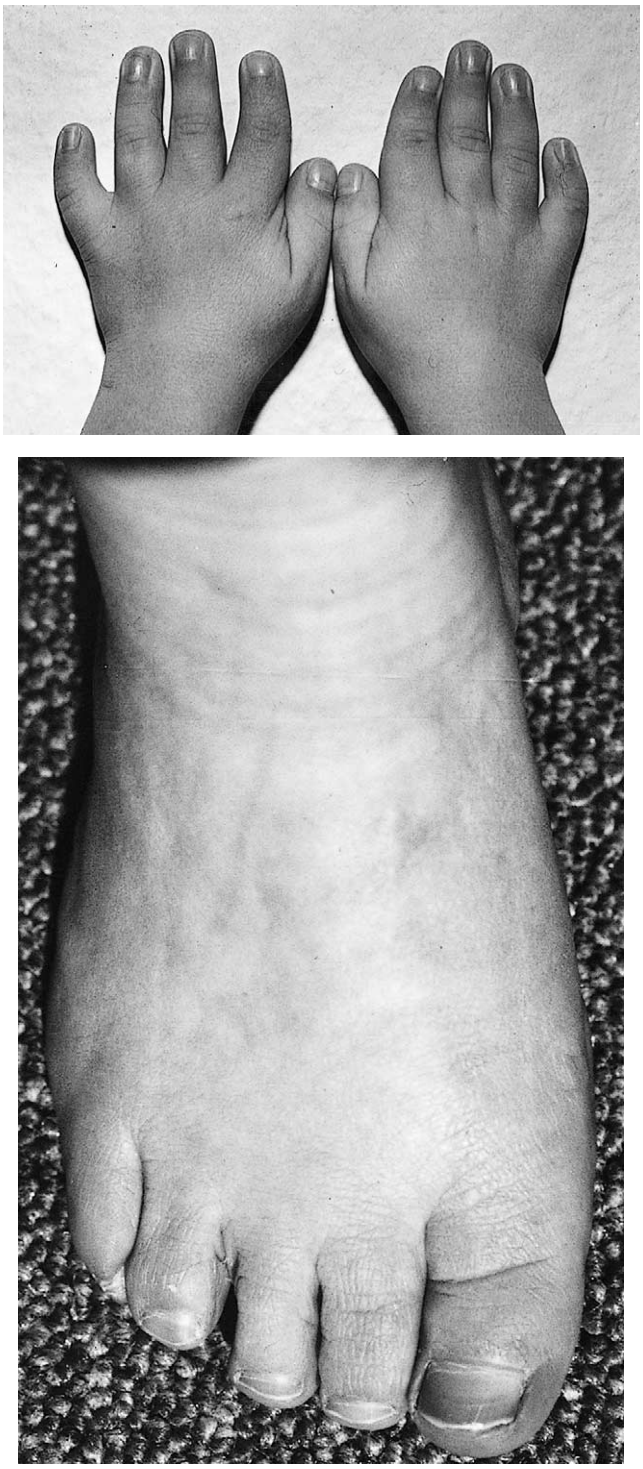

Fig. 3. Upper. Broad hands with brachydactyly and clinodactyly; Lower. broad feet with short toes.

plastic labia majora [4,16], rudimentary vagina and uterus [5,17], uretral orifice opening in the vagina; and anal stenosis [4], double gall bladder [5], hypoplastic adrenals at autopsy [10], soft skin [4], widely spaced nipples [8,11,15], diastasis recti [18], and umbilical and inguinal herniae [4,8,21]. Central nervous system anomalies have commonly included enlarged ventricles, sometimes necessitating shunting, and mild spastic diplegia, and rarely agenesis of the corpus callosum [8,9], and parietotemporal [10] or general [13] brain atrophy.

3. Differential diagnosis

Isolated Peters' anomaly, defined as the combination of a central corneal leukoma, absence of the posterior corneal stroma, absence of the membrane of Descemet, and strands running from iris and lens to the central posterior cornea, is in general a sporadic, non-genetic condition [25]. Genetically determined forms are usually autosomal recessive [26], but autosomal dominant forms are known too [27]. It has also been described to segregate in families together with other eye anomalies but without systemic abnormalities: as an autosomal dominant trait with early postnatal cataract, located at chromosome 11p13 [28]; as an autosomal dominant disorder with early postnatal cataract with microcornea [29]; and as an autosomal dominant disorder with microphthalmia and fusion of the upper and lower eyelids [30]. Peters' anomaly has been described in several chromosome anomalies: terminal deletion of chromosome 4p [31], mosaic trisomy 9 [31], deletion of 11q14 or q22 [32], trisomy 13 [31], terminal deletion of 18q [33], and ring 21 [34]. Temple et al. [35] described two cases with anterior chamber anomalies and also syndactylies, redundant skin, and hirsutism from a family with a translocation involving chromosome 2q37.2 and 7q36.3. Anterior chamber defects of the eye are also found in Rieger syndrome, SHORT syndrome, Abruzzo-Erikson syndrome, fetal alcohol syndrome, GMS syndrome, Marchesani-Weill syndrome, Michels syndrome, and Walker-Warburg syndrome [36]. The entity has been confused with Cornelia de Lange syndrome [4,15,20] and compared with Robinow syndrome [16,18,19]. Jung et al. [37] reported on a similar disorder, but the facial features were different, and the affected sibs also had cerebellar hypoplasia, tracheostenosis, and hypothyroidism. Moog et al. [38] mentioned two sibs with anterior chamber defects, mild mental retardation, diminished growth, hydrocephaly, and intracranial calcifications. Inheritance was probably autosomal recessive. Anterior chamber anomalies have been reported in two sibs who had in addition prenatal and postnatal growth deficiency, cleft lip and palate, radioulnar synostosis, arachnodactyly, long and bowed fibulae, talipes, heart defects, and early lethality [39]. It was thought to differ from Michels syndrome because of the absence of blepharophimosis, ptosis, and epicanthus inversus and presence of arachnodatyly and other skeletal symptoms. Peters' anomaly with brachymesomelia, but with different facial features, no brachydactyly, bowed radii, long thumbs, and normal intelligence was published by Kivlin et al. [40]. Appelmans et al. [41] described a case with microcephaly, growth delay, and mental retardation, but without any other abnormalities, and a case with mental retardation, large anterior fontanel, and

intestinal atresia. A family with three brothers with anterior chamber anomalies, mental retardation, microcephaly, growth delay, slender build, long face, multiple lentigines, and situs inversus was reported by Elmer et al. [42]. The father had anterior chamber anomalies and lentigines, the mother was mentally retarded. Two sibs were described with anterior chamber anomalies, corneal dermoids, and growth delay [43]. Ruprecht and Majewski [44] reported on two sisters with Peters' anomalies and arhina, and Tabuchi et al. [45] three sibs with Peters' anomaly and cardiac malformations including Fallot's tetralogy. Alkemade [25] and Heon et al. [46] described large series of patients with Peters' anomaly, of whom several had other solitary symptoms, and Kivlin et al. [2] and Holmstrom et al. [27] reviewed the literature for symptoms additional to anterior chamber anomalies.

4. Genetics

Peters' plus syndrome follows an autosomal recessive pattern of inheritance: multiple affected sib pairs have been described [1,2,4,6,8,10,11,16,21], there is an equal sex ratio (22 male, 29 female), there is no report of vertical transmission, and consanguinity has been found present in about one-third of the families [1,5,8–10]. Hennekam et al. [4] has pointed out that there is an increased rate of miscarriages and fetal losses at the end of the second or beginning of the third trimester, which may well indicate that the entity causes intrauterine death in some cases. The cause of death remains uncertain at present. The father of a Dutch unpublished case had an unilateral pre-auricular pit, which may be coincidence or expression of the heterozygous gene. In one case a familial and probably coincidental balanced translocation between chromosome 2q21 and 15q26.1 was found [2].

The cause of Peters' plus syndrome remains unknown. Isolated Peters' anomaly has been reported to be caused by mutations in *PAX6*, located at 11p13 [47], *PITX2* (or *RIEG1*), located at 4q25–26 [48], *PITX3*, located at 10q25 [49], and *CYP1B1* at 2p22 [50]. Although no case with Peters' anomaly and a mutated forkhead transcription factor gene *FKHL7* (locus: 6p26) has been described, many other forms of anterior chamber defects such as Rieger anomaly, Axenfeld anomaly, iris hypoplasia, and early-onset secondary glaucoma have been described with mutations in *FKHL7*, making it a good candidate gene for Peters' anomaly [51]. Expression studies have shown expression of *PITX2* in ocular mesenchyme of the mouse [52], both in cells originating from primitive mesoderm as from neural crest. The latter contributes to many structures in the eye, including stroma and endothelium of the cornea and the stroma of the iris. It has been suggested that mutations in both *PAX6* and *PITX2* cause Peters' anomaly through an altered neural crest development [48]. Anterior chamber anomalies were also reported in patients with a craniosynostosis (one with Pfeiffer syndrome, one with Crouzon syndrome), who had fibroblast growth factor receptor type 2 (FGFR2) mutations [53]. The same authors did not find mutations in seven patients with isolated Peters' anomaly and two patients with Peters' plus syndrome. FGFR2 is known to be implicated in the eye development, as are many other FGFRs and FGFs [54]. In the mouse expression of FGFR2 is found in the cornea, in the chick it is found in mesenchyme derived from neural crest cells around the optic cup. Both alternative spliceforms of FGFR2, kgfr and bek, are expressed in the developing lens [55], indicating a role in lens formation. Therefore, it seems well possible that the Peters' anomaly in Peters' plus syndrome, and, so, the total entity, is also caused by a disturbed neural crest development. As the number of genes involved in neural crest formation is vast, candidate genes will only be detected if gene localization has become possible, for instance through linkage studies. Such studies are at present in progress in our hospital.

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