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Peroxisome Biogenesis Disorders With Prolonged Survival: Phenotypic Expression in a Cohort of 31 Patients

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The peroxisome biogenesis disorders (PBDs) with generalized peroxisomal dysfunction include Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). There is clinical, biochemical, and genetic overlap among the three phenotypes, also known as Zellweger spectrum disorders. Clinical distinctions between the phenotypes are not sharply defined. Only limited sources are available to serve as a background for prognosis in PBD, especially in case of prolonged survival. We delineated the natural history of 31 PBD patients (age 1.2–24 years) through systematic clinical and biochemical investigations. We excluded classical ZS from our study, and included all patients with a biochemically confirmed generalized peroxisomal disorder over 1 year of age, irrespective of the previously diagnosed phenotype. The initial clinical suspicion, age at diagnosis, growth, development, neurological symptoms, organ involvements, and survival are summarized. Common to all patients were cognitive and motor dysfunction, retinopathy, sensorineural hearing impairment, and hepatic involvement. Many patients showed postnatal growth failure, 10 patients displayed hyperoxaluria of whom 4 had renal stones. Motor skills ranged from sitting with support to normal gait. Speech development ranged from non-verbal expression to grammatical speech and comprehensive reading. The neurodevelopmental course was variable with stable course, rapid decline with leukodystrophy, spinocerebellar syndrome, and slow decline over a wide range of faculties as outcome profiles. At the molecular level, 21 patients had mutations in the *PEX1* gene. The two most common PEX1 mutations were the G843D (c.2528G→A) missense and the c.2097insT frameshift mutation. Patients having the G843D/G843D or the G843D/c.2097insT genotypes were compared. Patients homozygous for G843D generally had a better developmental outcome. However, one patient who was homozygous for the "mild" G843D mutation had an early lethal disease, whereas two other patients had a phenotype overlapping with the G843D/c.2097insT group. This indicates that next to the PEX1 genotype other yet unknown factors determine the ultimate phenotype.

KEY WORDS: peroxisome biogenesis disorders; Zellweger syndrome; neonatal adrenoleukodystrophy; infantile Refsum disease; natural history; prolonged survival; *PEX1* gene

INTRODUCTION

Peroxisomal disorders are a heterogeneous group of inherited metabolic diseases characterized by a deficiency of one or more functions of peroxisomes [Gould et al., 2001; Wanders et al., 2001]. The disorders can be classified into two major groups. In the first group there is a defect in peroxisome biogenesis (PBDs) which is associated with either a generalized or multiple loss of peroxisomal functions. In the second group there is deficiency of a single peroxisomal enzyme. The generalized PBDs have a varied symptomatology with at least three phenotypes, their names assigned before the association with peroxisomes was recognized: Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD) [Kelley et al., 1986; Poll-The et al., 1987; Steinberg et al., 1999]. The three disease phenotypes, referred to as the Zellweger spectrum, are characterized by the inability to import peroxisomal matrix proteins into peroxisomes. Factors required for this import of proteins are now referred to as peroxins (pex). Peroxisomal matrix proteins are targeted to peroxisomes via one of two different peroxisome targeting signals, PTS1 and PTS2, respectively. The failure in these conditions to form peroxisomes leads to impairment of many peroxisomal functions including the β-oxidation of very long-chain fatty acids (VLCFA), long branched-chain fatty acids (pristanic acid), and of di- and tri-hydroxycholestanoic acid (bile acid precursors), formation of polyunsaturated fatty acids (PUFA), plasmalogen biosynthesis (etherphospholipids), phytanic acid α-oxidation, and pipecolic acid oxidation. There is marked genetic heterogeneity among the PBDs with at least 11 different genetic complementation groups [Moser et al., 1995; Gould and Valle, 2000]. Most patients (60–70%) belong to complementation group 1, which results from mutations in

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the *PEX1* gene, and mutations in PEX1 can account for the full spectrum of phenotypes seen in these patients. Two frequent mutations have been identified in the *PEX1* gene: a missense mutation, G843D (c.2528G→A) [Portsteffen et al., 1997; Reuber et al., 1997] and a frameshift mutation, c.2097insT [Maxwell et al., 1999]. Patients homozygous for the G843D mutation usually show a mild IRD phenotype, whereas patients homozygous for c.2097insT present the severe ZS phenotype. Patients compound heterozygous for G843D/c.2097insT show a phenotype of intermediate severity.

Here, we describe the major clinical and biochemical findings in a cohort of 31 PBD patients older than 1 year, and relate their developmental phenotypes to the two most common PEX1 mutations.

PATIENTS AND METHODS

Patients with classical ZS were excluded from the study by inhibiting patients with a survival of less than 1 year to enter the study. Thus, only patients (n = 31) with a generalized PBD and survival after the first year were included. Age at diagnosis was defined as the age at the time of biochemical confirmation of the diagnosis. Developmental outcome could not be simply measured as intelligence quotient. Development in PBD is limited by: (1) retinopathy and other ophthalmological handicaps including refraction anomalies and occasionally cataracts, (2) sensorineural hearing impairment, (3) specific neurological defects, (4) complicating medical handicaps, foremost liver and renal failure. Because the overall outcome was considered to be more important than individual scores for each handicap, we devised a compound developmental score for patients surviving more than 4 years (24 patients) based upon statural motor control, hand control, verbal development, and visual development. Statural motor control contributed 1 point for unsupported sitting, and 1 for unsupported walking. Intentional hand control contributed 1 point. On the verbal scale 1 point is contributed by each of the following attainments: active hearing or intentional vocalizing (1 point), 3 or more words used intentionally (1 point), telegram sentences used for communication (1 point), grammatical language including storytelling (1 point), comprehensive reading (1 point). Visual acuity between 1 and 10% (0.1) contributed 1 point and visual acuity over 10% (>0.1) 2 points. Together a maximum of 10 points can be attained. Because the ability to read is included, the maximum score for patients of 4 years is expected to be 9 instead of 10. The cut-off of visual acuity at 10% has been made for practical purposes, defining a limit above which visual handicap does not pose severe restrictions on daily activities. Peroxisomal investigations in body fluids and fibroblasts were performed according to standard procedures in our laboratory [Schrakamp et al., 1985; Wanders et al., 1995a,b; Vreken et al., 1998]. Complementation analysis was used to assign patients to the PEX1 group, which was followed by molecular analysis to identify the G843D (c.2528G→A) and c.2097insT mutations. These mutations were related to the developmental achievements.

Neuroimaging performed in the majority of the patients will be reported separately. Standard treatment for 20 patients included administration of docosahexaenoic acid, in some cases also arachidonic acid, as oral supplements and phytanic acid restriction. Further medication included vitamin E and vitamin K.

RESULTS AND DISCUSSION

Biochemical Results

The biochemical results are summarized in Table I. All patients presented elevated plasma very long-chain fatty acids and all, but one patient had also elevated plasma di- and trihydroxycholestanoic acid. Plasma phytanic acid and pristanic acid values were normal in a minority of the patients. Plasmalogen levels in erythrocytes were found to be deficient only in about half of the patients. Erythrocyte docosahexaenoic acid levels, however, were decreased in a significant number of patients. This deficiency may be progressive, and, therefore, normal levels may occur in very young patients.

TABLE I. Biochemical Characteristics of 31 PBD Patients of 1 Year and Older

	N with abnormal results	%
Plasma		
Very long-chain fatty acids	31	100
Di- and tri-hydroxycholestanoic acid	30	97
Phytanic acid[a]	26	84
Pristanic acid[a]	25	81
Erythrocytes		
Plasmalogen level	16	52
Docosahexaenoic acid (C_{22}:6ω3)	26	84
Urine		
Hyperoxaluria	10	32
Fibroblasts		
Plasmalogen synthesis	31	100
$C_{26:0}$ β-oxidation	31	100
Pristanic acid β-oxidation[b]	23	100

[a]Phytanic acid and pristanic acid are derived from dietary sources and may therefore vary depending on the dietary intake.
[b]Performed in 23 PBD fibroblast lines.

A systematic survey for increased oxalate excretion revealed abnormal results in 10/31 patients (32%); among these cases, four patients presented renal stones. Alanine:glyoxylate aminotransferase is a liver-specific peroxisomal enzyme, which becomes cytosolic when peroxisome biogenesis is defective as is the case in generalized peroxisomal disorders, but hyperoxaluria and nephrocalcinosis/urolithiasis have been reported only in three patients with a generalized peroxisomal disorder [Danpure et al., 1994; Barth et al., 2001].

Fibroblast studies confirmed a generalized peroxisomal disorder in all 31 patients.

Demography

The patient group consisted of 31 individuals with a generalized peroxisomal disorder from 27 families. Sixteen were males. Three unrelated patients were born to consanguineous parents. Gestational age was 37 weeks in three patients, and between 38–43 weeks in 28 patients. Caesarean section was performed for absence of contractions in one, maternal fever in one, and maternal exhaustion or meconium stained fluid in two. APGAR scores were 8–10. Age at follow-up was 1.2–24 years of age. Twenty four patients were older than 4 years. Virtually all patients were from North-Western European ancestry; no prevalence of isolated rural communities was recorded in the birth places of the patients.

Survival

In this PBD population, there is a significant subset of patients who live beyond the age of 4 (Fig. 1). Therefore, parents should be counseled that a child of at least 1 year of age and with a non-progressive course has 77% probability to survive to school age. The mean length of survival for the 9 deceased patients was 8.0 years (1.2–22.5 years).

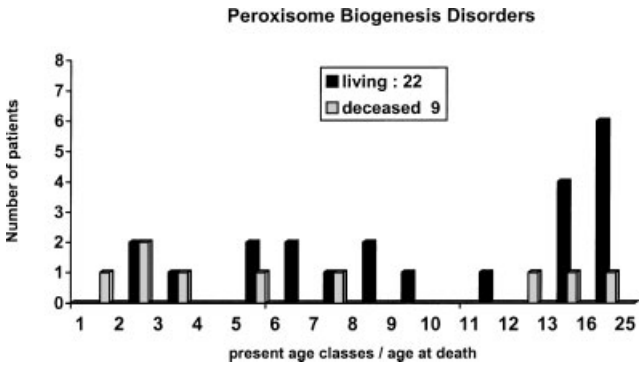

Fig. 1. Number of peroxisome biogenesis disorder (PBD) patients plotted against present age classes or age at death.

Death was attributed to consequences of respiratory problems, dehydration and shock, renal failure due to nephrocalcinosis, liver failure, and gastrointestinal hemorrhage due to gastric varices (Table II). There is insufficient information in two patients. Although the figures are still small, no increase of the survival period seems to be achieved over the past decades. No effective treatment has been designed, hence any therapeutic approach is supportive.

Cause of Suspicion and age at Diagnosis

Using the measurement of plasma very long-chain fatty acids, phytanic acid, pristanic acid and di- and tri-hydroxycholestanoic acid, as well as plasmalogen levels in erythrocytes as screening protocol, followed by detailed peroxisomal studies in cultured fibroblasts, we established the diagnosis of a generalized peroxisomal disorder in all the 31 patients (Table I). The age of the biochemical diagnosis was between 1 month and 14.5 years.

The mean was 2.2 years at diagnosis, whereas clinical manifestations were present soon after birth to 3 years of age (Table III). Medical records revealed failure to thrive associated with or without another clinical symptom as first cause of concern in 39% (12/31). Characteristic craniofacial features such as a large anterior fontanelle and Down syndrome-like facies were mentioned to be the cause of suspicion in 13% (4/31). Only one patient presented neonatal seizures and was ultimately diagnosed as neonatal onset leukodystrophy. None of the patients presented severe hypotonia as initial manifestation as is seen in classical ZS. Thus the initial clinical presentation was generally non-specific. It stresses the importance of testing for peroxisomal functions by biochemical analyses in every patient with failure to thrive and uncertainty about hearing and vision in infancy or early childhood.

TABLE II. Causes of Death in 9 Patients With PBDs With Survival of at Least >1 Year

Causes	Age (years)	Number
Respiratory	2.9; 3.1	2
Respiratory and seizures	1.3	1
Dehydration and shock	5	1
Liver failure	12.4	1
Renal failure (renal stones)	15	1
Gastrointestinal hemorrhage	22.5	1
Unknown	2.8; 7.9	2

TABLE III. Initial Clinical Symptom and Age at Diagnosis in 31 PBDs With Survival of at Least >1 Year

Symptom	Number	Age at diagnosis (months)
Failure to thrive	9	1–24
Failure to thrive and hepatosplenomegaly	1	6
Failure to thrive and jaundice	1	16
Failure to thrive and visual failure	1	8
Visual failure	3	17–60
Neonatal seizures and leukodystrophy	1	8
Visual failure and jaundice	1	6
Nystagmus	1	36
Hearing impairment	5	12–174
Down syndrome-like dysmorphism	2	16–26
Large fontanelle	2	30–48
Loss of unsupported sit	1	19
Behavior disorder	1	21
Gait imbalance	1	92
Younger sibling diagnosed	1	42

Growth and Nutritional Status

Ranges of measures in the newborn period were: birth weight, 2280–4250 g (males: mean 3253 g; females: mean 3124 g); birth length, 48–54 cm (males: mean 51.6 cm; females: mean 50.5 cm), and head circumference, 33–35 cm (males: mean 34.4 cm; females: mean 33.4 cm). On average, birth measures were about 0 SD. Unlike ZS, none of the patients needed prolonged nasogastric tube feeding in the first months of life. However, two patients had to be fed exclusively by tube feedings for failure to thrive at a later time and subsequently underwent gastrostomy. These patients died at the age of 1.2 and 7.8 years. One required temporary nasogastric tube feeding between 6 and 6.5 years, while another needed the tube feeding during the last 6 months of life before she died at 2.8 years.

Many patients showed postnatal growth failure. Linear growth was between −2.5 and −6.5 SD in 42% (13/31) and weight to length less than −2.5 SD was observed in 39% (12/31). Growth of the head circumference was increasing in one patient from −3 SD at the age of 6 months to −2 SD at 8 years, whereas in another it was decreasing from +1 SD at 2 years to −5 SD at the age of 15 years.

The length of the two adult patients, aged 20 and 24 years, was 0 SD and −2 SD, respectively.

Development

Developmental achievements are known to be limited in patients with PBDs. However, no follow-up studies of developmental skills that are and are not attained at a certain age have been reported. We examined the compound developmental score for PBD patients surviving beyond the age of 4 years (24 patients) by monitoring their achievements detailed in Table IV. Developmental skills such as sitting without support, intentional hand use, walking without support, and active hearing/intentional vocalizing were attained by most patients (>75%) in this population. Patients sat without support at 9–30 months and walked without support at 14–66 months. More advanced developmental skills such as speaking in phrases (grammatical language/storytelling) and reading were seen only in a minority, 21% (5/24) and 4% (1/24), respectively.

TABLE IV. Developmental Skills in 24 PBDs Older Than 4 Year of Age

Skill	Milestones acquired in number of patients	%
Sit without support	23	96
Walking without support	18	75
Intentional hand use	23	96
Active hearing/intentional vocalizing	19	79
Three or more words intentionally used	14	58
Telegram style grammar/active language	14	58
Grammatical language/storytelling	5	21
Comprehensive reading	1	4
Visual acuity 1–10% (<0.1)*	15	62
Visual acuity more than 10% (>0.1)*	9	37

*Test results reflect visual acuity after correction for refraction anomalies for both eyes or best eye, and are expressed as Snellen equivalent of Teller cards or formal acuity test.

Neurological syndromes were seen in a number of patients: (1) neonatal onset leukodystrophy: 1; (2) late onset white matter disease: 4; (3) spinocerebellar syndrome: 1.

Those who were able to attend school were all assigned to institutional schools with educational plans to cope with the cerebral developmental as well as sensory handicaps.

Development Related to Gene Mutation

The majority of patients (68%; 21/31) belonged to complementation group 1 resulting from mutations in the *PEX1* gene. About 71% (17/24) of those who lived beyond age 4 years had PEX1 mutations. Nine of these 17 patients (14 families; 3 families with 2 affected siblings) were homozygous for the G843D mutation, three were compound heterozygotes for the G843D/c.2097insT mutations, four were compound heterozygotes with G843D/other mutation, and one patient had two other mutations. On the basis of these results, developmental achievements of patients surviving beyond 4 years of age were plotted against mutations in the *PEX1* gene (Fig. 2). Previous mutational analyses of PEX1 in complementation group 1 patients had shown that those who were homozygous for the G843D mutation tended to be associated with the mild end of the ZS phenotypic spectrum, whereas patients homozygous for the c.2097insT mutation displayed the severe ZS phenotype [Reuber et al., 1997; Collins and Gould, 1999; Maxwell et al., 1999; Walter et al., 2001]. None of the PEX1 patients older than 4 years was homozygous for the c.2097insT frameshift mutation. This is consistent with the observation that the c.2097insT mutation is associated with a severe forms of disease. Seven of the 9 patients (>4 years) who were homozygous for the G843D mutation indeed had the milder phenotype exhibiting a compound developmental score of more than 6 points. The most significant finding of our study is that two patients who were homozygous for the "mild" mutation attained less than 6 points in the compound developmental score system similar to three patients who were compound heterozygous for the c.2097insT mutation and the G843D missense allele. In addition, two siblings who were compound heterozygous for the G843D mutation and another mutation displayed different clinical severity, one (18.7 years) attained 10 points whereas her younger brother (13.2 years) reached only 4 points. It is also interesting that one patient who had not attained any development and died at 1.2 year of age appeared to be homozygous for the G843D mutation.

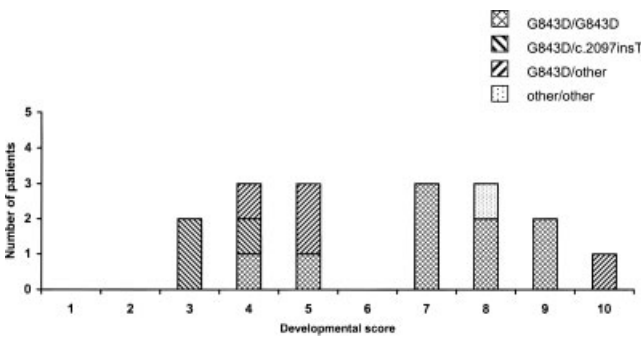

Fig. 2. Distribution of compound developmental scores according to genotypes of 17 PEX1 patients older than 4 years.

Seizures

Seven patients (23%) developed seizures. The average age at which the first seizure activity was noted was 0–2.7 years. Seizure types included oral automatisms, myoclonic, atonic, tonic, tonic-clonic, and infantile spasms with hypsarrhytmia on electroencephalography (3/7). Multiple seizure types were seen in the same patient over time. Among these 2/7 presented progressive late-onset cerebral white matter disease and died at the age of 5 and 2.8 years [Barth et al., 2001]. One patient presented neonatal seizures and neonatal onset leukodystrophy, and died at 3.1 years.

Eye

All 31 patients presented a severe visual handicap, ranging from complete blindness at birth to a corrected vision of 20–30% by appropriate glasses. Only 9/24 children older than 4 years had a visual acuity more than 0.1 (Table IV). Refractive anomalies, mostly high myopia, were frequent. The history of the onset of poor vision has not been documented in most of the patients. Between 0–5 months some eye contact was documented in 10/31 (32%) children. Between 4 months and 4 years strabismus was present in 17/31 (55%) and nystagmus in 12/31 (39%). In 7/31 (23%) pursuit eye movements have never been achieved. Retinopathy with a depressed or extinguished electroretinogram (ERG) was noted in 26/31 (84%), cataracts in 3/31 (10%), and optic nerve atrophy in 17/31 (55%). In our opinion every patient should be examined with follow-up testing and also by visual electrodiagnostic methods (ERG, VER), which offer objective assessment of sensory visual pathway function. One has to be aware that establishing visual function in PBDs is complex because of the limited developmental and communication skills, and the hearing impairment of the patients. We have, therefore, chosen to express test results of the visual acuity in patients older than 4 years as Snellen equivalent of the Teller cards. The test results reflect the best corrected visual acuity for both eyes or best eye. We distinguished between visual acuity less or more than 10% (Table IV).

Ear

Patients with PBDs have a significant sensorineural hearing impairment. Indeed, all 31 patients had a hearing impairment recognized between 2 and 24 months. At least in 13% (4/31) the impairment progressed as concluded from brain auditory evoked potentials. Twenty seven patients used hearing aids with beneficial effects in at least 67% (18/27). Acceptance and even dependence on the device was a factor in positive evaluation of the results. One patient underwent cochlear implantation with a (subjectively) positive effect.

Liver, Spleen, and Kidney

The liver was initially enlarged in 68% (21/31). Of those who had hepatomegaly, 33% (7/21) had no liver enlargement any more at an older age. The first clinical suspicion for a peroxisomal disorder was prolonged neonatal jaundice in association with failure to thrive in one patient, and hepatosplenomegaly with failure to thrive in another. Of those who underwent a liver biopsy (about one-third) hepatic involvement ranged from almost normal to fibrosis and/or cirrhosis. In one patient a gallstone was detected by ultrasound at 9 years. Ten patients (32%) presented hyperoxaluria of which four of them had renal stones. Treatment with pharmacologic doses of pyridoxine had no effect on the oxalate excretion. Intervention measurements were initiated in the four patients with-renal stones such as copious fluid intake, dietary restriction of oxalate-rich food, and an inhibitor of calcium oxalate crystallization orally. Death occurred in one patient at 15 years of age attributed to the consequences of renal failure caused by renal stones, and one needed surgical removal of stones at the age of 7.2 years. Hyperoxaluria should be considered in all patients with a generalized peroxisomal disorder. Renal cysts were observed in one patient who also had renal stones.

Miscellaneous

In addition to the mostly mild facial dysmorphic features (high forehead 18/31; epicanthal folds 7/31), 64% (20/31) presented abnormal and attached ear lobules (Fig. 3). Some patients had no facial dysmorphism (Fig. 4). One patient had her first tooth eruption after 2 years of age, and 33% (8/24) of the patients older than 4 years developed problems with dentition such as malpositioned teeth, and enamel hypoplasia. None of the patients had a structural congenital heart defect; one patient had a patent ductus arteriosus.

Four patients experienced non-traumatic fractures (age 5 months, 9 months, 1 year, 11 years) and one needed surgical treatment for hip dislocation at 8 years. Cutaneous syndactyly of the second and third toe was observed in one patient. About one-third of patients presented valgus foot deformity. Two of the 16 male patients had undescended testes.

CONCLUSIONS

Remarkable progress has been achieved in the understanding of the disorders of peroxisome biogenesis, and peroxisomal disorders continue to contribute to the understanding of organelle assembly and protein import. Once a diagnosis is made, patients should be followed carefully in order to help anticipate medical problems and need for supportive care. It must be noted that we used the term “mild” here only to make a difference from classical ZS, and that virtually all patients with the “milder” phenotypes are significantly disabled. Although effective therapy still remains an elusive goal, knowledge about the pathogenesis will hopefully contribute to this end.

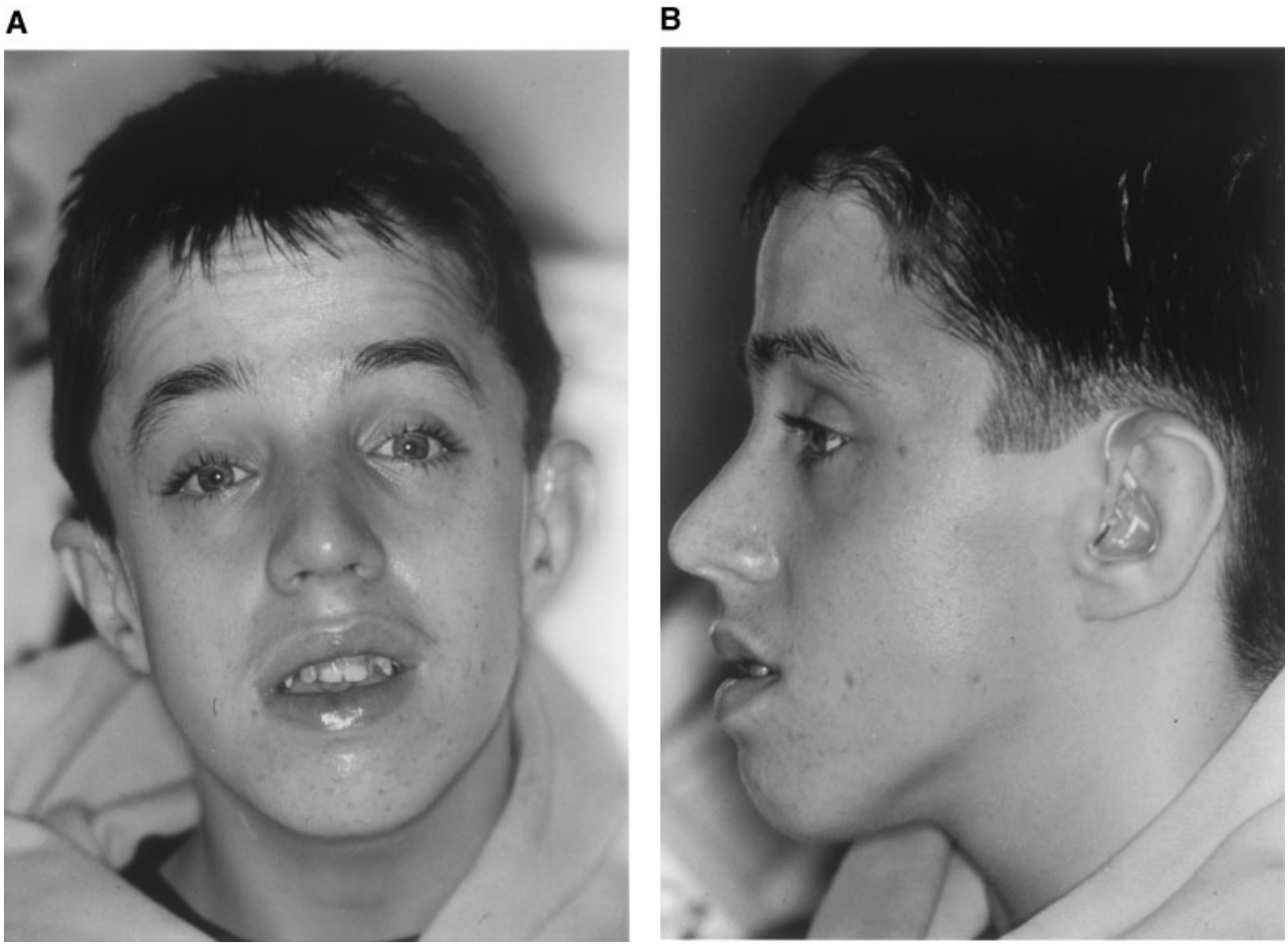

Fig. 3. PBD patient at 17.5 years. **A**: Note the facial features, very mild facial dysmorphia. **B**: Attached ear lobule. (Courtesy Dr. Hugo Heymans, Amsterdam).

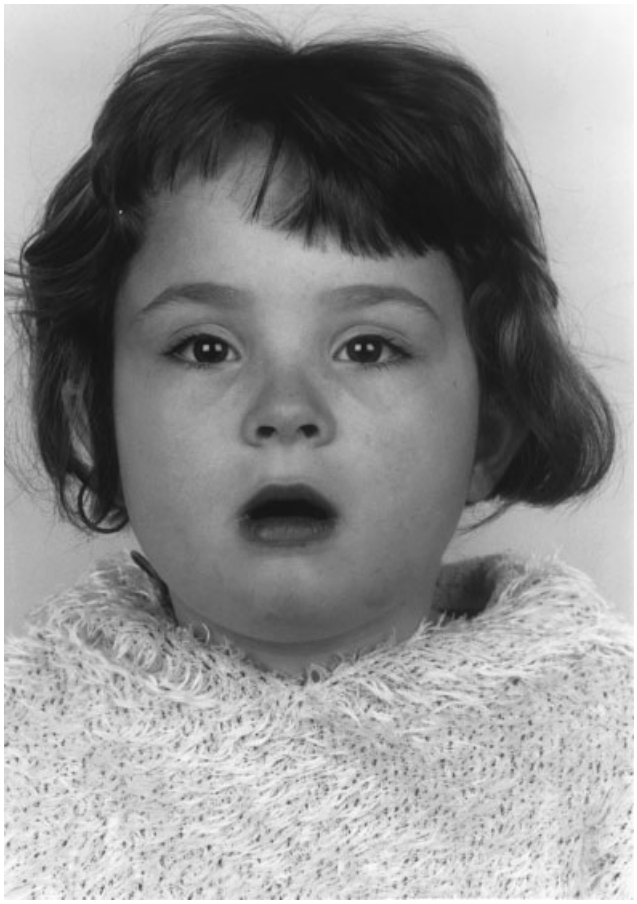

Fig. 4. PBD patient at 6.5 years. Absence of facial dysmorphism.

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