

Majewski Osteodysplastic Primordial Dwarfism Type II (MOPD II): Natural History and Clinical Findings

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A description of the clinical features of Majewski osteodysplastic primordial dwarfism type II (MOPD II) is presented based on 58 affected individuals (27 from the literature and 31 previously unreported cases). The remarkable features of MOPD II are: severe intrauterine growth retardation (IUGR), severe postnatal growth retardation; relatively proportionate head size at birth which progresses to true and disproportionate microcephaly; progressive disproportion of the short stature secondary to shortening of the distal and middle segments of the limbs; a progressive bony dysplasia with metaphyseal changes in the limbs; epiphyseal delay; progressive loose-jointedness with occasional dislocation or subluxation of the knees, radial heads, and hips; unusual facial features including a prominent nose, eyes which appear prominent in infancy and early childhood, ears which are proportionate, mildly dysplastic and usually missing the lobule; a high squeaky voice; abnormally, small, and often dysplastic or missing dentition; a pleasant, outgoing, sociable personality; and autosomal recessive inheritance. Far-sightedness, scoliosis, unusual pigmentation, and truncal obesity often develop with time. Some individuals seem to have increased susceptibility to infections. A number of affected individuals have developed dilation of the CNS arteries variously described as aneurysms and Moya Moya disease. These vascular changes can be life threatening, even in early years because of rupture, CNS hemorrhage, and strokes. There is variability between affected individuals even within the same family. © 2004 Wiley-Liss, Inc.

KEY WORDS: MOPD II; primordial dwarfism; intrauterine growth retardation; prominent nose; postnatal growth deficiency; bone dysplasia

INTRODUCTION

Over the last two decades a specific syndrome of severe intrauterine growth retardation (IUGR) has been recognized. It was probably first explicitly described in the medical literature by Brizard et al. [1973]. However, Seckel's 1960 monograph on so called "bird-headed" dwarfs includes at least one affected individual [Seckel, 1960] and a clear description of an affected woman was present in the circus archives prior to that time [Drimmer, 1973]. Majewski et al. [1982a] defined Majewski osteodysplastic primordial dwarfism type II (MOPD II) within a series of articles on Seckel syndrome and other specific syndromes of primordial dwarfism [Majewski and Goecke, 1982; Majewski et al., 1982b]. They characterized it as having severe IUGR with relatively proportionate head size at birth, but progression to severe microcephaly, progressive bony dysplasia, and characteristic facies and personality.

All together at least 26 reports of affected individuals have been published in the medical literature [Brizard et al., 1973; Anoussakis et al., 1974; Pasquino and Iannaccone, 1978; Boscherini et al., 1981; Tsuchiya et al., 1981; Majewski and Goecke, 1982, 1998; Majewski et al., 1982b; Poznanski et al., 1983; Toudic et al., 1983; Verloes et al., 1987; Willems et al., 1987; Herman et al., 1991; Shebib et al., 1991; Sugio et al., 1993; Théau and Maroteaux, 1993; Al Gazali et al., 1995; Masuno et al., 1995; Spranger et al., 1996; D'Angelo et al., 1998; Halder et al., 1998; Tekin et al., 2000; Fukuzawa et al., 2002; Kantaputra, 2002; Seymen et al., 2002; Nishimura et al., 2003], in which 27 affected individuals have sufficient clinical information on natural history to be included in this report. This report describes the natural history of MOPD II based on the 27 published cases and 31 additional unpublished affected individuals.

Some reports of possible cases of MOPD II are not included because the clinical information is insufficient [Seymen et al., 2002; Nishimura et al., 2003] or because affected individuals were reported who were too large at birth or grew to be too tall to be typical for MOPD II [Cervenka et al., 1979; Tsuchiya et al., 1981; Skinner, 1991; Sugio et al., 1993; Lin et al., 1995]. The challenge now is to try to define the outer limits and spectrum of MOPD II and to search for the responsible gene.

Historical Perspective

The first person of whom we are aware with MOPD II is Lucia Zarate. Lucia was born in Mexico in 1864. She was said to be "7 inches long" and weighed "8 ounces" at birth. She moved to the United States of America at the age of 12 years, at which time she was sexually mature and 20 inches in height, but weighed only 5 pounds. She worked for the Barnum and Bailey Circus for many years as one of its major attractions. She was described as cheerful, loquacious, and beloved by the circus troupe. She is thought to have been the smallest woman who ever lived [Drimmer, 1973]. She is reported to have died of

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exposure in a snowstorm at the age of 26 years when the circus train on which she was traveling tried to cross the Rocky Mountains and became stuck in the snow.

A second historical reference has been made to Princess Wee Wee, who was of African-American heritage and known to be extremely small. The records and pictures suggest that she had MOPD II, but little medical information is available [personal communication, Lucas and Ernestine, 1990].

Seckel [1960] published a monograph presenting information on a heterogeneous group of 15 individuals with IUGR, microcephaly, short stature, and unusual craniofacial features. At least one and possibly two of these individuals (Cases 5 and 10) had features compatible with MOPD II; however, insufficient information was reported in order to be sure of the diagnosis.

In the medical literature, probably the first report of an individual clearly affected with MOPD II was by Brizard et al. [1973]. However, the report by Brizard was in French and did not come to general attention. Similarly, non-English publications of Anoussakis et al. [1974] and Pasquino and Iannaccone [1978] described individuals with very similar features of severe IUGR and severe postnatal growth restriction. Boscherini et al. [1981] reported the Italian individual again, in English this time. Majewski et al. [1982a] and other authors reviewed reported cases of Seckel syndrome and distinguished three specific types of primordial osteodysplastic dwarfism (e.g., primordial = the features were present during early in utero development, osteodysplasia = abnormalities in bony growth; and dwarfism = disproportionate short stature) and distinguished them from Seckel "bird-headed" dwarfism [Majewski and Goecke, 1982, 1998; Majewski et al., 1982a,b; Majewski, 1992] in which more severe microcephaly was present at birth, and the IUGR was less severe, as was postnatal growth deficiency. MOPD II became a distinct and distinguishable entity. Subsequently, the original Majewski types I and III have been recognized to reflect different ages of the same condition [Majewski et al., 1982a; Winter et al., 1985; Haan et al., 1989; Meinecke and Passarge, 1991; Meinecke et al., 1991] involving CNS malformations, sparse hair, dry skin, and more severe skeletal dysplasia. A "new" third type of MOPD has been reported characterized by distinct bony and facial changes [Bondeson, 1992; Majewski, 1992].

The original Majewski reports [Majewski and Goecke, 1982; Majewski et al., 1982a,b] were important since there had been a great deal of confusion in the medical literature concerning conditions with the combination of IUGR and microcephaly. Majewski et al. [1982b] made the point that the type II individuals at birth were not severely microcephalic in proportion to their bodies, but became so over time. At birth the head circumference is small, but in proportion to the body size; both are approximately the size of a normal 28-weeks gestation infant when born at term. Majewski et al. [1982b] also described the characteristic facial features and the progressive bony dysplasia.

Poznanski et al. [1983] clarified the radiological changes of two affected individuals who had been reported previously by Pasquino and Iannaccone [1978] and again by Boscherini et al. [1981]. Willems et al. [1987] reported a family with consanguinity and suggested that there might be an autosomal recessive basis for the disorder and Verloes et al. [1987] reported another consanguineous family with two affected siblings. Herman et al. [1991] reported an additional female and Shebib et al. [1991] reported a girl from a consanguineous Saudi Arabian family who had only 11 ribs and had very little response to growth hormone therapy.

By 1995, when Masuno et al. reported a Japanese girl with the typical facies, the clinical features of MOPD II had begun to be more clearly defined. When Al Gazali et al. [1995] reported another consanguineous family from the United Arab

Emirates, it was suggested that there might be certain ethnic groups which were predisposed to having affected children with MOPD II.

Spranger et al. [1996] reported a male with severe knee dislocations who also had hypospadias, micropenis, a horse-shoe kidney, hypoplasia of the corpus callosum, mildly dilated ventricles, and increased intracranial pressure with premature closure of cranial sutures. The boy also had microlarynx and misplaced upper lobe bronchus. The possibility was raised that there might be a broad spectrum of anomalies seen within what was now recognized as a specific condition. In that same article, the authors also reviewed the types of progressive radiologic features which are present.

Majewski and Goecke [1998] summarized the previous reports and added one consanguineous and one non-consanguineous Turkish family as well as a European boy who had been given growth hormone therapy without remarkable improvement in growth. Also Halder et al. [1998] reported a family from India with consanguinity who also demonstrated delayed myelination and minor CNS abnormalities. D'Angelo et al. [1998] reported the neurosurgical treatment of multiple intracranial aneurysms in an individual with typical features of MOPD II. This raised the possibility that these unusual CNS vascular changes were part of the natural history of MOPD II.

Tekin et al. [2000] reported on an African-American boy with subglottic stenosis and typical physical and natural history features. By the year 2000, 9 males and 14 females had been reported. Eight of these families were consanguineous and one family had two affected sibs. There had also been four deaths reported: one with gastroenteritis at 8 months, one with vomiting episodes at 6 years, one who died suddenly in a manner compatible with a CNS bleed at 13 years, and still another of unknown causes. An autopsy report by Fukuzawa et al. [2002] reported a MOPD II girl who died after an episode of vomiting (infections versus seizures) at 6.5 years. No CNS abnormalities were found on autopsy except patchy thickening of the pia matter. No vessel abnormalities were observed; however, unusual ballooning of chondrocytes and an increased number of pancreatic islet cells were observed. Kantaputra [2002] reported affected siblings emphasizing their dental abnormalities and suggesting a different name.

METHODS

Review of the literature produced 27 cases [Brizard et al., 1973; Anoussakis et al., 1974; Pasquino and Iannaccone, 1978; reported again by Boscherini et al., 1981; Majewski et al., 1982a; Toudic et al., 1983; and by Poznanski et al., 1983; Verloes et al., 1987; Willems et al., 1987; Herman et al., 1991; Shebib et al., 1991; reported again by Théau and Maroteaux, 1993; Al Gazali et al., 1995; Masuno et al., 1995; Spranger et al., 1996; D'Angelo et al., 1998; Halder et al., 1998; Majewski and Goecke, 1998; Tekin et al., 2000; Fukuzawa et al., 2002; Kantaputra, 2002; Nishimura et al., 2003] with sufficient clinical and natural history information to be sure of the diagnosis and to contribute to defining the frequency of various features. The authors of the articles were recontacted to update clinical information and to provide additional comments on features not mentioned in the original reports.

In North America, a number of physicians interested in short stature began to recognize additional individuals with this disorder. Some of the interest arose because affected individuals were part of television shows. A network of communication began both among several physicians and geneticists and many of the families. It was also recognized that affected individuals have very characteristic personalities, physical features, and heights at various ages together with a very slow rate of growth. Affected individuals were described as "peas in

a pod” by one of the television hosts. Indeed, they do have striking similarities. Through the Little People of America, together with a parent-organized group, and by referrals from a number of physicians, it has been possible to accumulate clinical information on an additional 31 affected individuals. Several other referred individuals, were deemed to more likely have the syndrome described by Buebel et al. [1996] or to have the Meier–Gorlin syndrome [Bongers et al., 2001; Shalev and Hall, 2003].

This article is aimed at defining the present state of knowledge about natural history and various system involvement and is intended to encourage reporting of single cases which have additional unusual features or combinations of features. This work has been possible only through the collaboration and cooperation of many physicians and many families who filled out questionnaires and responded to letters of inquiry about specific features (see “Acknowledgments”).

It is becoming clear that what was once thought to be an extremely rare condition is probably not so rare. Perhaps this is related to increased survival because of improved neonatal care. Efforts to identify the responsible gene are underway.

There is adequate information available on a total of 58 individuals (males 22, females 36) to warrant including them in this report. Individuals were included if they had typical growth patterns, evidence of bony dysplasia over time, visible either by X-ray changes or the development of disproportion, and typical facial features by photograph or examination. Additional helpful features were small dysplastic teeth, high squeaky voice, and the development of abnormal, patchy, and increased pigment; however, all of these features can be seen in other disorders. For the purpose of trying to clearly define the phenotype, the presence of very large or very small ears, absent patellae, large teeth, or atypical growth pattern led to exclusion. The relative rate and age of developing various clinical

features and the severity of those features varied among affected individuals and even varied within the same family.

Growth data were plotted separately for males and females, and for published and newly ascertained cases. Since there were no striking differences among the four groups, the growth data have been combined. Separate growth curves are available upon request.

RESULTS AND DISCUSSION

Pregnancy

Pregnancies with affected children are often complicated with nausea and vomiting, pre-eclampsia, bleeding, fetal decelerations, and premature delivery. No common teratogens or environmental exposures have been reported. The placenta is usually quite small, being half to three-quarters normal size for gestation. With the advent of ultrasound, pregnancies have been monitored more carefully and the IUGR has often led to induced early delivery. The mean delivery age is 35 weeks (with the range from 28 weeks to post-term).

Growth

Severe IUGR is a consistent feature of this condition. It appears from the experience of the few pregnancies which have been monitored with ultrasound at an early stage that the onset, or at least the recognition, of growth deficiency occurs somewhere between 12 and 14 weeks of the pregnancy and the growth deficiency becomes progressively more severe over the remainder of the pregnancy. If birth is at term, the birth weight is, for practical purposes, always less than 1,500 g and usually more in the range of 1,100–1,300 g at term (Fig. 1). The recorded range of weight at birth is between 450 and 1,600 g.

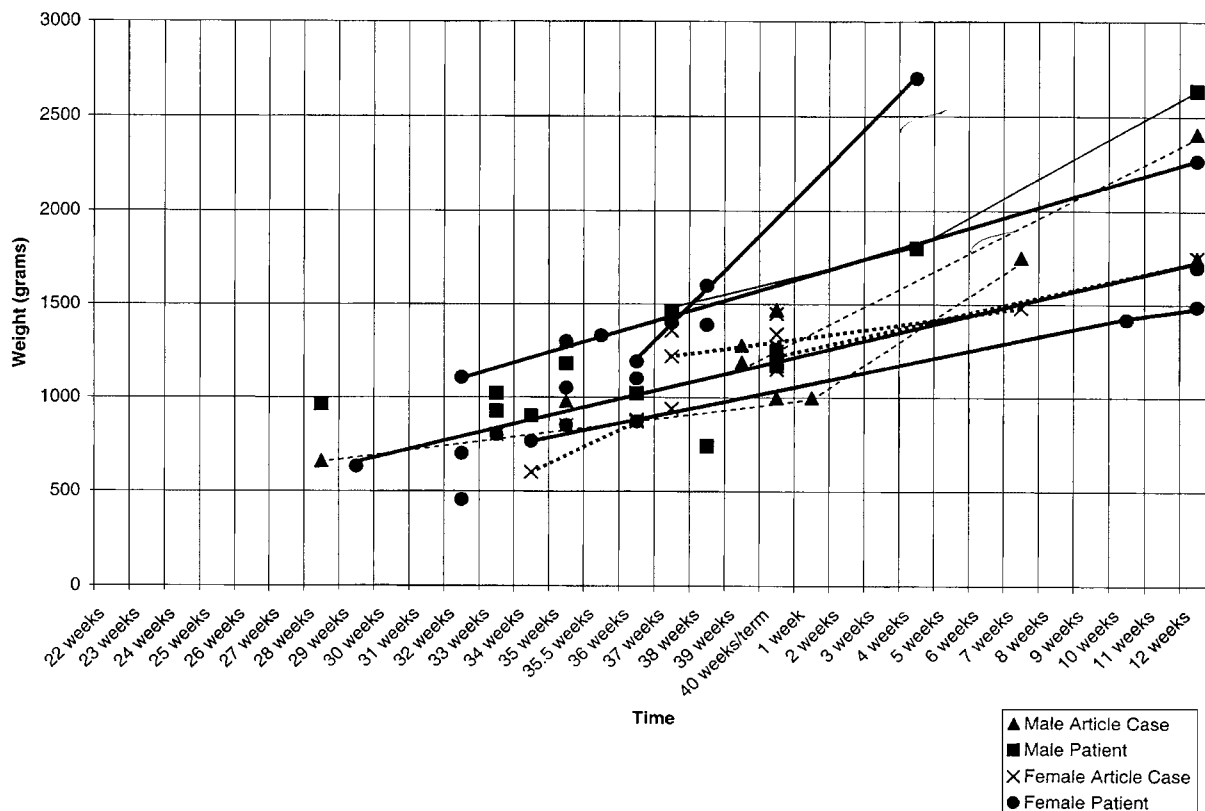


Fig. 1. Birth weights (and early subsequent growth information when available) at various gestational ages for all reported cases.

Only one individual who we believe to have MOPD II was said to have a birth weight above 1,500 g. He was a male who weighed 1,860 g at term. He had an affected sister who weighed only 1,220 g at term delivery. A range of birth weight is seen at all gestational ages, and is severely compromised at all ages. A birth weight above 1,500 g should lead to questioning the diagnosis. Postnatal weight curves are seen in Figure 4.

Like birth weights, birth lengths are markedly diminished. The birth lengths have been recorded between 30 and 40 cm at term. Any infant with birth length longer than 40 cm at term probably represents a different condition (many standard deviations below the mean) (Fig. 2). Post-pubertal final height is almost always below 100 cm (Fig. 5).

Occipital frontal circumference (OFC) at birth ranges between 22 and 29 cm and usually appears proportionate for body size, but often is recorded as microcephaly, which, of course, it is, for gestational age (Fig. 3). Post-pubertal OFC which have recorded ranges between 38.5 and 41 cm (Fig. 6).

Many MOPD II children were born prematurely, both spontaneously and because of induction of delivery due to increasing evidence of fetal distress. The mean gestational age at delivery is 35 weeks and the average birth weight is approximately 1,000 g. Because of the severe IUGR, expected date of confinement (EDC) has occasionally been fallaciously adjusted when intrauterine size seemed so small.

The mean birth weight at term for a MOPD II infant would be normal for that of a 28-week-old fetus. Similarly, mean term length is that of a normal 28-gestational-week-old fetus. The mean OFC for a term MOPD II infant is also proportionate for a 28-week-old fetus. Thus, there is a proportionate IUGR, with preservation of normal head size for body size, but, of course, not for the normal body size at birth of a normal term

pregnancy. Although MOPD II individuals have been called microcephalic, it is important to remember that the proportions are relatively normal at birth and subsequently that the head size becomes disproportionately small for body size after birth. Most affected infants do not reach normal newborn size until between 2 and 5 years of age (see Figs. 1–6). If an affected newborn's measurements are plotted on the newborn tables, males and females are slightly different, with males very slightly larger; but all of the affected children are very severely proportionately intrauterinely growth-retarded at birth.

It is difficult to plot postnatal growth since it is so severely deficient, falling away from the third centile norms at a dramatic rate. There continues to be deceleration in the length and height compared to normal, and there is even more deceleration of the OFC. Over time, the individuals become more disproportionate, particularly involving the head size and the distal limbs.

Radiographic examination of bone age usually shows dysharmonic maturation of centers and a retarded bone age. The retardation is usually read as between 2 and 5 years behind chronological age. Since MOPD II includes a skeletal dysplasia involving the epiphyses and metaphyses, the bone age probably does not really reflect bone maturation. Dental eruption age suggests that there may actually be precocious physiologic advancement of bone maturation. Indeed, precocious puberty is often seen, particularly in affected females, with breast development at age 7 years and menses by age 9 years.

Adult post-pubertal heights are almost always below 100 cm, and always below 110 cm (Fig. 5). Growth often stops by 12 years of age although a few males have continued to grow until 16 years of age. The growth measurements, reflecting

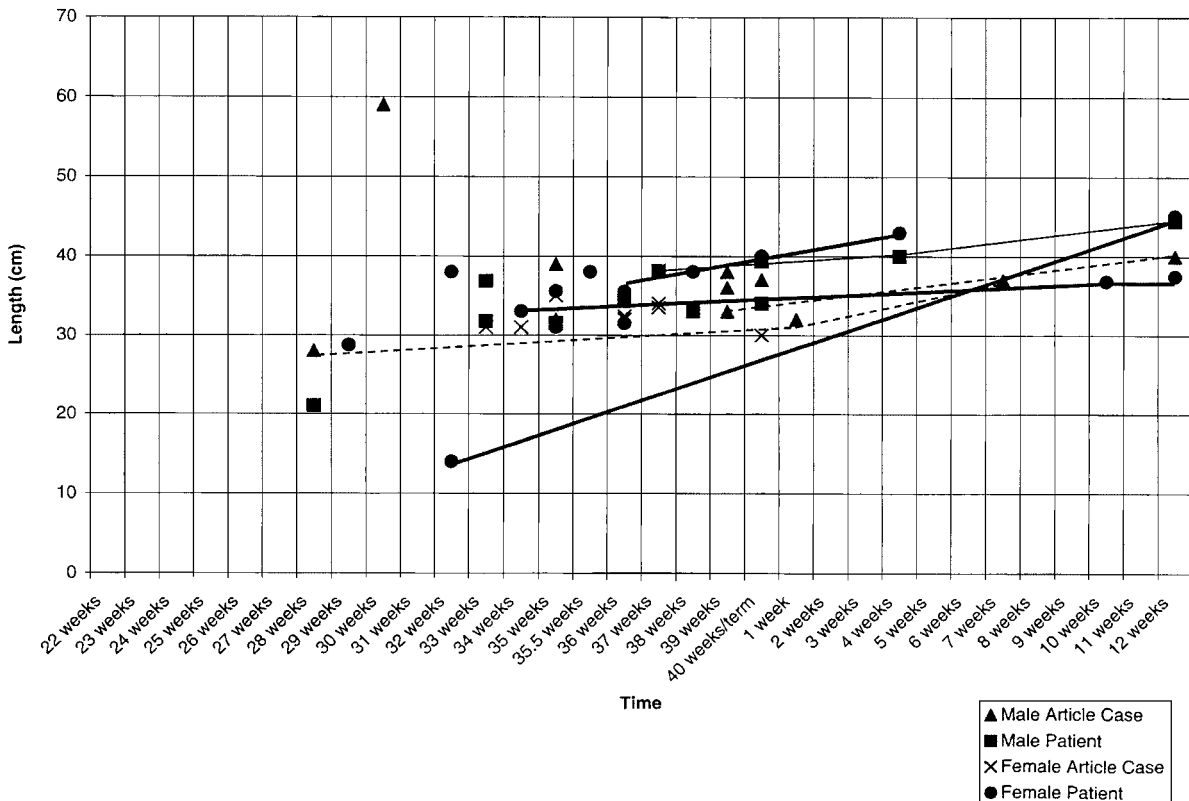


Fig. 2. Birth lengths (and early subsequent growth information when available) at various gestational ages for all reported cases.

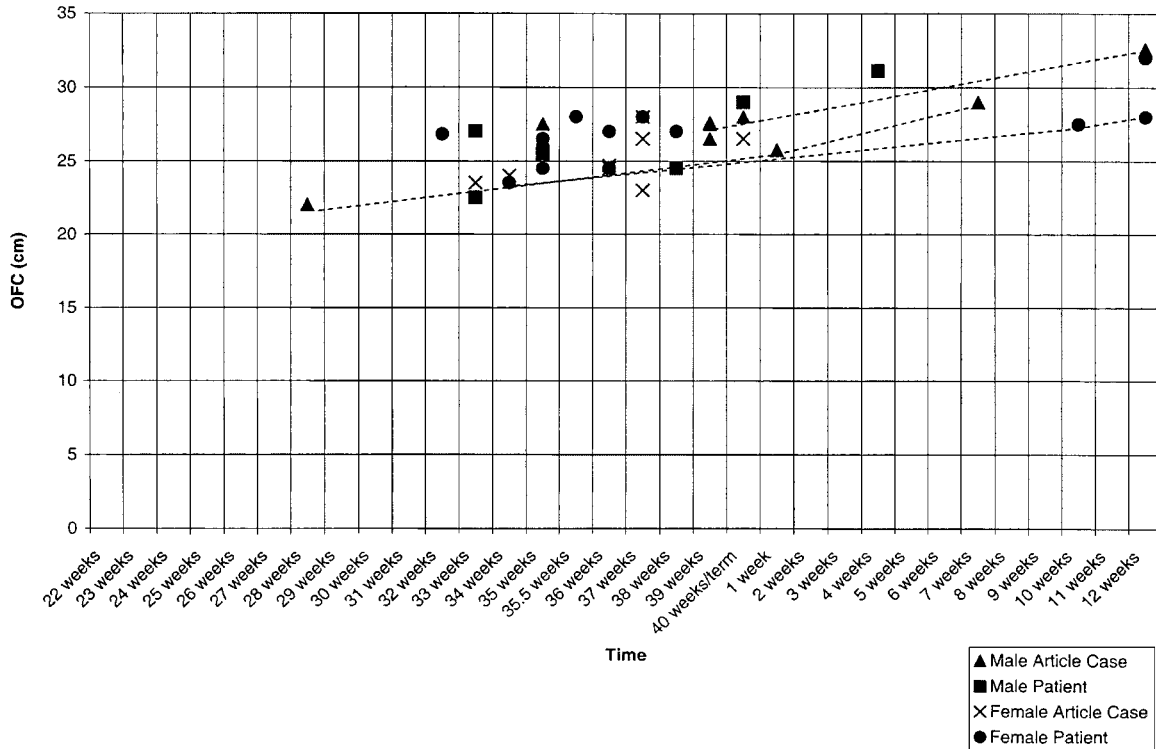


Fig. 3. Birth occipital frontal circumference (OFC) (and early subsequent growth information when available) at various gestational ages for all reported cases.

very severe intrauterine and postnatal growth retardation, are one of the major characteristics of MOPD II. An individual without this typical growth pattern probably does not have MOPD II (e.g., below 40 cm and 1,500 g at birth and below 100 cm at maturation).

There are several reports [Cervenka et al., 1979; Tsuchiya et al., 1981; Lin et al., 1995] of males who are larger and have more mental retardation than typical MOPD II affected individuals. These reports may represent another disorder, be affected by the same disorder or represent different alleles.

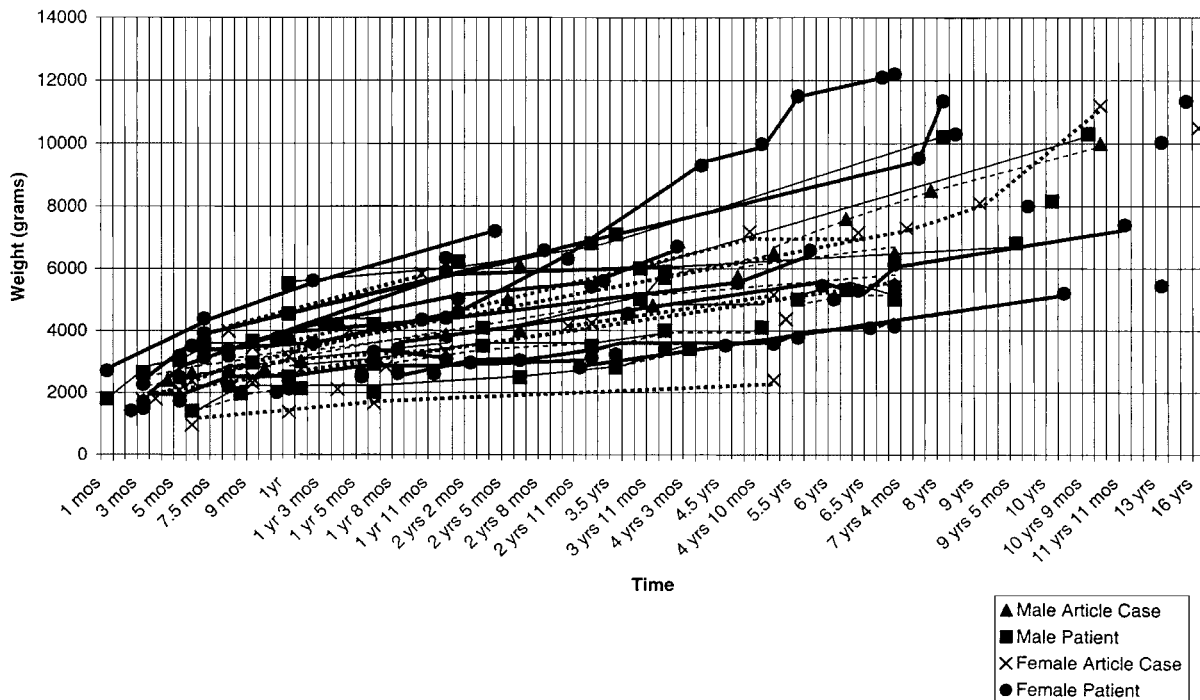


Fig. 4. Post birth weights at various ages. Male and female data are combined.

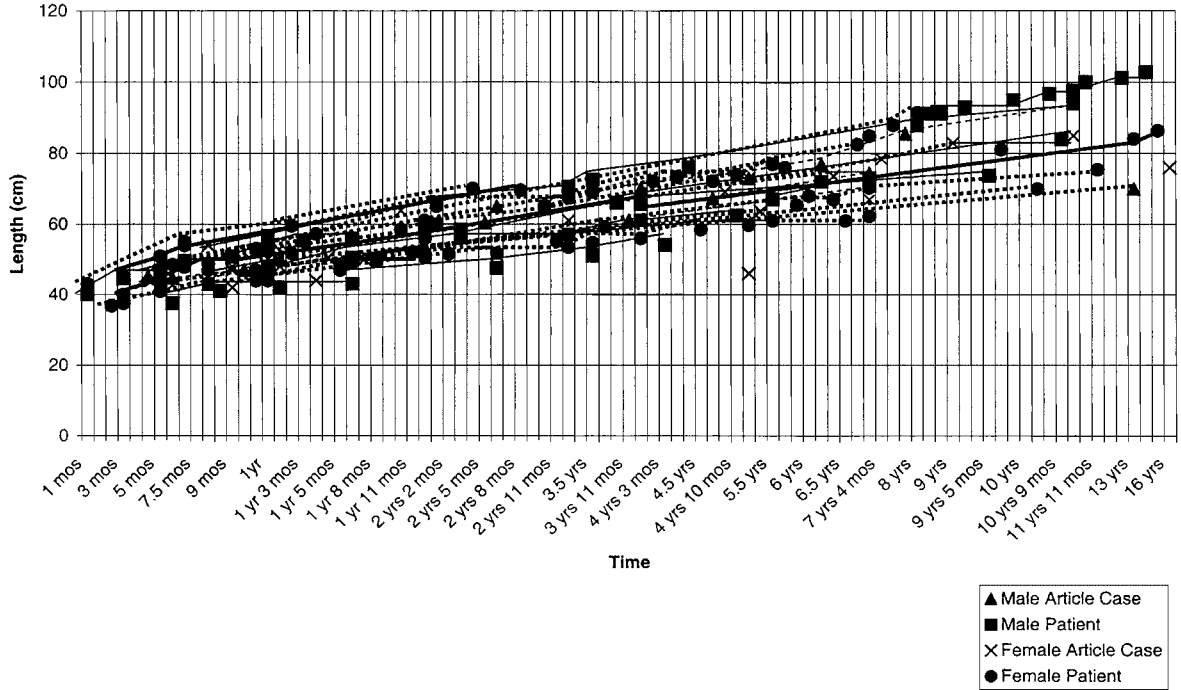


Fig. 5. Post birth length and height for age. Data includes males and females and multiple known data points are linked for an individual.

Other reports of females by Buebel et al. [1996] (Case 1) and Sugio et al. [1993] are also larger than expected for typical cases of MOPD II, with ptosis, scoliosis, and broad nose, and may also represent affected individuals or a different disorder. We have left such cases out of this analysis to try to clarify the phenotype.

Response to Growth Hormone

Almost half of affected individuals with MOPD II on whom we have records have been treated with growth hormone (a few more males than females). In spite of normal GH testing and no response to treatment, some individuals have been treated for

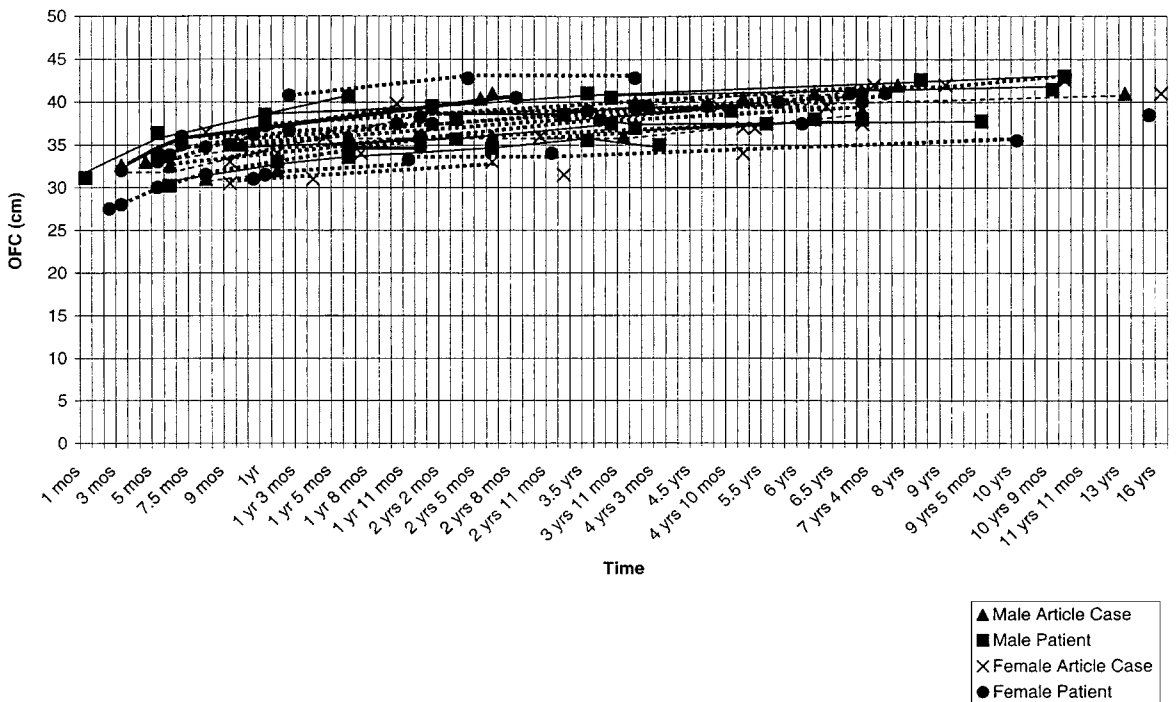


Fig. 6. Post birth OFC for age. Data includes males and females and multiple known data points are linked for an individual.

many years, one for 6 years. There appears to be very little response to growth hormone therapy, although in some cases, an initial small "spurt" in growth may be seen. This increase in growth rate is never more than a few centimeters of spurt and it always tapers off, back to the typical growth pattern for MOPD II within a year. One individual was said to have growth hormone deficiency on testing, but had normal somatomedin I levels; however, even this MOPD II affected individual did not have a good response to GH therapy. The age of initiation of GH therapy and the birth size do not seem to affect response. It is not yet clear whether those individuals receiving growth hormone will achieve better adult height; however, this seems unlikely. Interestingly, individuals treated with growth hormone seem to develop increased pigment and café au lait spots, which are usually seen at a later age or at puberty in other MOPD II individuals (see below). Initially in reviewing MOPD II cases, there was some concern that GH therapy might aggravate the CNS vascular lesions, but this does not seem to be the case since six of the MOPD II affected individuals with CNS vascular anomalies never received growth hormone therapy.

Puberty

Precocious puberty has occurred in 6 of the 21 females who are over 8 years of age. Proportionate breast development and regular menses occur with puberty. Some girls have shown signs of puberty as early as 7 years and started menses often by 9 years. No hormonal studies have been done in these individuals. Menses are reported to be normal. No pregnancies have been documented in adult women with MOPD II. The one affected woman who is 37 years did not have precocious puberty, but did have cessation of menses at 25 years, suggesting premature menopause. No other gynecologic abnormalities have been noted except that many females are said to have underdeveloped labia and prominent clitoris. One girl, who died at 19 years of age, was hirsute and had polycystic ovaries.

The few males on whom there are data have had onset of puberty between 11 and 13 years of age with deepening of voice, facial hair growth, onset of acne, and nocturnal emissions. Of the 9 older males (13 males are less than 11 years of age), precocious or delayed puberty does not appear to be a problem.

However, of the total group of 22 males 1 had hypospadias and 6 have cryptorchidism. The penis is described as small, but proportionate.

In several of the children, particularly males, the areolae appear to be large, at least in relation to the size of the chest (Fig. 7). In some children, the nipples seem to have increased pigment even at a very young age. The breast development that has occurred in females, however, has been in proportion to body size.

Feeding and Ponderal Growth

At least 80% of all affected infants have feeding problems. They are able to take only small amounts and need frequent feedings. Vomiting and poor sucking are frequent. As infants, frequent night feedings are required. For some infants with respiratory problems, feeding is a real challenge during the first year. Nutrition may need to be provided through a nasogastric feeding tube or G-tube. One child was born with ileal atresia and another child developed intestinal necrosis as an infant.

During the first few years of life, the body is usually slender and with decreased subcutaneous fat. Starting as early as 6 months of age, but more often between 3 and 5 years of age, truncal obesity develops in 80% of affected individuals (Fig. 8a). The limbs are usually spared; however, as the bony dysplasia progresses, the limbs often appear disproportionately short (Fig. 8a). The truncal obesity may accelerate at puberty. If affected individuals do not develop truncal obesity, they may appear prematurely aged.

Head Size and CNS Growth

Head size is always small for age. Proportionate to the body at birth, the rate of growth of the head decelerates during the first year and relative microcephaly develops (as well as head size compared to norms for age) (Fig. 6).

One fourth of affected individuals have documented structural or myelination abnormalities of the CNS. Decreased or abnormal myelination patterns were seen in four females and one male. Enlarged ventricles were seen in three males and one female which may imply that there are relatively fewer neurons present than expected for relative head size, or



Fig. 7. Relatively large areolae and pigmentary anomalies. Note generalized increase in pigment, café au lait spots, and irregular areas of decreased pigment.

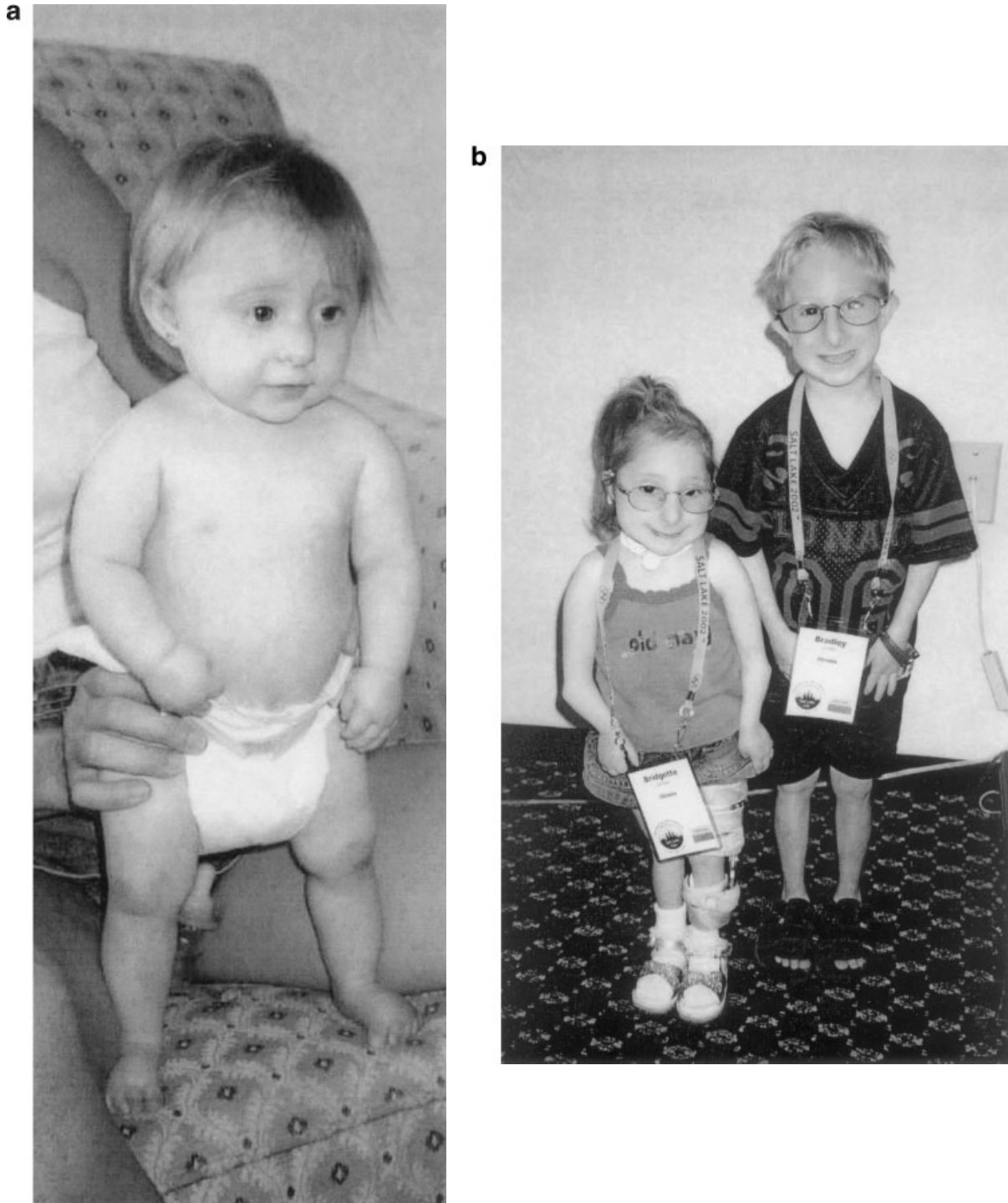


Fig. 8. **a:** Relatively proportionate short stature with developing truncal obesity age 13 months. **b:** Sister (13 years old) and brother (9 years old). Sister has developed relative disproportion with mesomelic shortening of arms and dislocated elbows. Both have short hands with tapering fingers. Note brace for dislocated knee, tracheostomy, and hearing aid. The younger brother is obviously much taller than his older sister.

possibly atrophy in some cases. Three males and one female had abnormal gyral patterns. Several affected individuals had cysts of the corpus callosum and sella areas and hypoplasia of the corpus callosum. The sella is often described as large. Patchy thickening of the membranes covering the brain were observed both on MRI and at autopsy in several individuals.

Premature closure of fontanelles and cranial sutures has been reported. One case, a male, had premature craniosynostosis which improved with surgical treatment. Two females had increased markings on the inner table of the skull, but no treatment. Craniosynostosis should be screened for during the first 2 years.

CNS Vascular Anomalies

Eleven of the 58 individuals reported here have had apparent overgrowth of the CNS vessels (5 males, 6 females). Four affected individuals have died from rupture of CNS vessels (2 males, 2 females) at ages 13–25 years. One had a stroke with residual hemiparesis a year before her death. Imaging to demonstrate the CNS vascular supply has revealed abnormalities of arterial structure in asymptomatic and symptomatic individuals. These vascular changes have been variously described as Moya Moya disease, tortuous vessels, or multiple cerebral aneurysms [D'Angelo et al., 1998; Nishimura et al., 2003]. It is not clear whether this type of abnormality is congenital or progressive. One girl had a documented intrauterine vascular accident with vessel abnormalities and then repeated strokes from 3 years of age. A boy had a stroke at 32 months and abnormal vessels seen thereafter. One 25 year old man who had magnetic resonance angiography (MRA) which showed a small single lesion died of intracranial hemorrhage shortly thereafter. Two individuals have been treated in the standard way with clips, such that intracranial aneurysms have not gone on to rupture [D'Angelo et al., 1998]. Many individuals of all ages with MOPD II have had careful imaging studies with no CNS vascular abnormalities found including the 37 year old woman.

Individuals affected with MOPD II should be monitored with CNS vascular imaging studies for the development of this type of vascular anomalies starting at least by mid-childhood since three affected individuals became symptomatic before 4 years of age. Relatively, males may be more prone to the problem. The CNS vascular anomalies appear to be accelerated by puberty; however, the natural history is not yet clear. There are several individuals with MOPD II in their 20s and even into their 30s without any sign of this problem.

Personality

Parents relate that affected individuals have sociable and outgoing personalities. In addition, they are described as hyperactive during infancy and childhood. There may be problems related to short attention span and easy distractibility. Parents suggest consistency and firmness are helpful. Many parents describe difficulty with change including displays or flares of anger. Most of the children have had very poor sleep patterns in the first few years with frequent awakening and often requiring supplementary feedings during the night. Because of their pleasant personalities, most families thoroughly enjoy affected individuals and readily make adjustments to accommodate their special needs.

Developmental Delay

It is hard to properly evaluate development by normal standards. Most affected individuals are delayed compared to their sibs and families but do have excellent social skills and manage surprisingly well. Some children apparently have normal intelligence with only a learning disability. Intelligence quotient (IQ) are usually in the 50–90 range and may well correlate with familial IQ or have been affected by nutritional deficiency if feeding problems were severe in infancy. Although affected individuals may be slow to develop understandable language, they tend to babble, repeat, and talk rapidly and continuously in a way their families understand. Many affected individuals can converse in several languages.

Motor delay may be seen early. If there are no feeding problems or illness, early developmental milestones may be normal. Thus, developmental landmarks may be normal or delayed by as much as 50%; however, almost all affected individuals walk, communicate, and manage many daily living skills in spite of their severe short stature. Some affected

individuals have finished high school and some have even attended college. None have been able to live independently—partly because of their small size and the need for protection from unintentional injury.

Craniofacial Features

Very distinctive craniofacial features are present in MOPD II. The affected newborn appears proportionate but already has unusual and distinctive facial features for an infant. The forehead is usually neither tall, nor receding. It is important to distinguish this from other types of IUGR in which the head is disproportionately small at birth and may have a very short and/or posteriorly sloping forehead. A great deal of confusion has occurred between the various types of IUGR with microcephaly. In most, the head is disproportionately small at birth as compared to MOPD II. In the past, Seckel syndrome was used to encompass conditions which have severe microcephaly at birth. In Seckel syndrome, as differentiated by Majewski et al. [1982a] and Thompson and Pembrey [1985], the head size is usually disproportionately small at birth and becomes even more so over time. The forehead in Seckel syndrome is described as receding and the ears are relatively large. Several types of IUGR also have distinctive facies and/or prominent noses. In addition, there is variability, even within a MOPD II family, which can lead to confusion. Nevertheless, the craniofacies of MOPD II is distinctive and includes specific features of the nose, mouth and jaw, teeth, and ears. The facial expression is somewhat pensive at rest, but pulls up into a wide grin with animated expression making the nose more prominent (Fig. 9).

Nose. An important craniofacial feature in MOPD II is the prominent nose. This is not always obvious in the newborn period, but it becomes quite distinctive over the first year. The nasal root is elevated and broad, and the bridge is wide, particularly in the mid-nose (Figs. 9 and 10). The root is continuous with the eyebrow and the supraorbital ridges which are rather hypoplastic. The broad bridge of the nose ends in a broad, but hypoplastic tip of the nose. There is hypoplasia of the alae nasi, which are both thin and underdeveloped leading to small nostrils. Because of ethnic differences the alae nasi may appear broad, but when compared to the parents are thin. The tip of the nose is full, but not prominent and as the nose grows, the tip often dips somewhat under, giving, in lateral view a curve to the bridge of the nose as it comes down to the tip. The columella often lies below the alae nasi. The philtrum may appear long, but is actually small for age. The distinctive nose is quite different from unaffected members of the family.

Mouth and jaw. The mouth may appear small, but with facial movement, usually appears normal for the size of the face. The midface appears long. The jaw may be small. In infancy, micrognathia is often present. It may be moderate, but is more often mild. The cheeks are often prominent (Fig. 10). There are no difficulties with jaw opening. The tongue seems to function normally and is in proportion to the mouth. The palate may appear high. None of the 58 individuals included here has clefting of the palate.

Eyes. The eyes usually appear quite prominent during childhood. The palpebral fissures may be a normal length for age which also makes the eyes look large. If the palpebral fissure is short, the iris looks large. The shallow orbits contribute to the prominent appearance. With age, the eyes are less prominent and may even seem slit-like (Fig. 9e). There may be a mild downslanting to the palpebral fissure. The globes are normal to small. With aging, the eyeball does not grow in length and so becomes relatively short, and in more than half the children, farsightedness develops requiring glasses. Glasses may be needed as early as 3 years of age and, in most affected individuals, by 5 years of age. The glasses often have to be constructed specifically for the child because of the

a



b



c



d

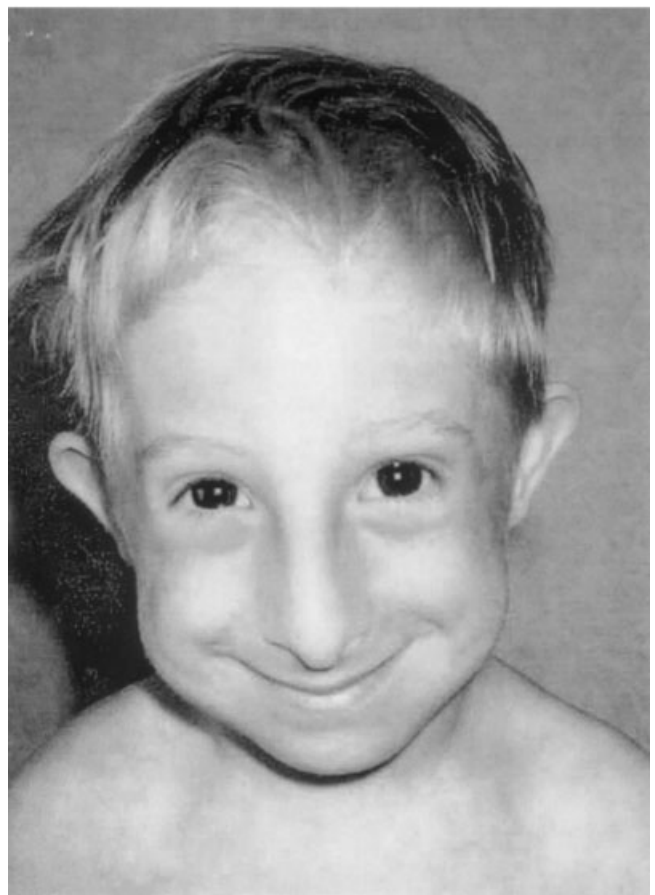


Fig. 9. Craniofacial features—frontal (a) 11 month old girl, (b) 13 month old girl, (c) 7 year old girl, (d) 9 year old boy, (e) 13 year old boy, (f) 37 year old woman; lateral (g) 13 month old girl, (h) 9 year old boy, (i) 13 year old girl, (j) 37 year old woman. Note the broad nose, hypoplastic tip, and thin alae nasi. The ears are proportionate to head size with attached lobules. The mid face is long. Eyes appear large.

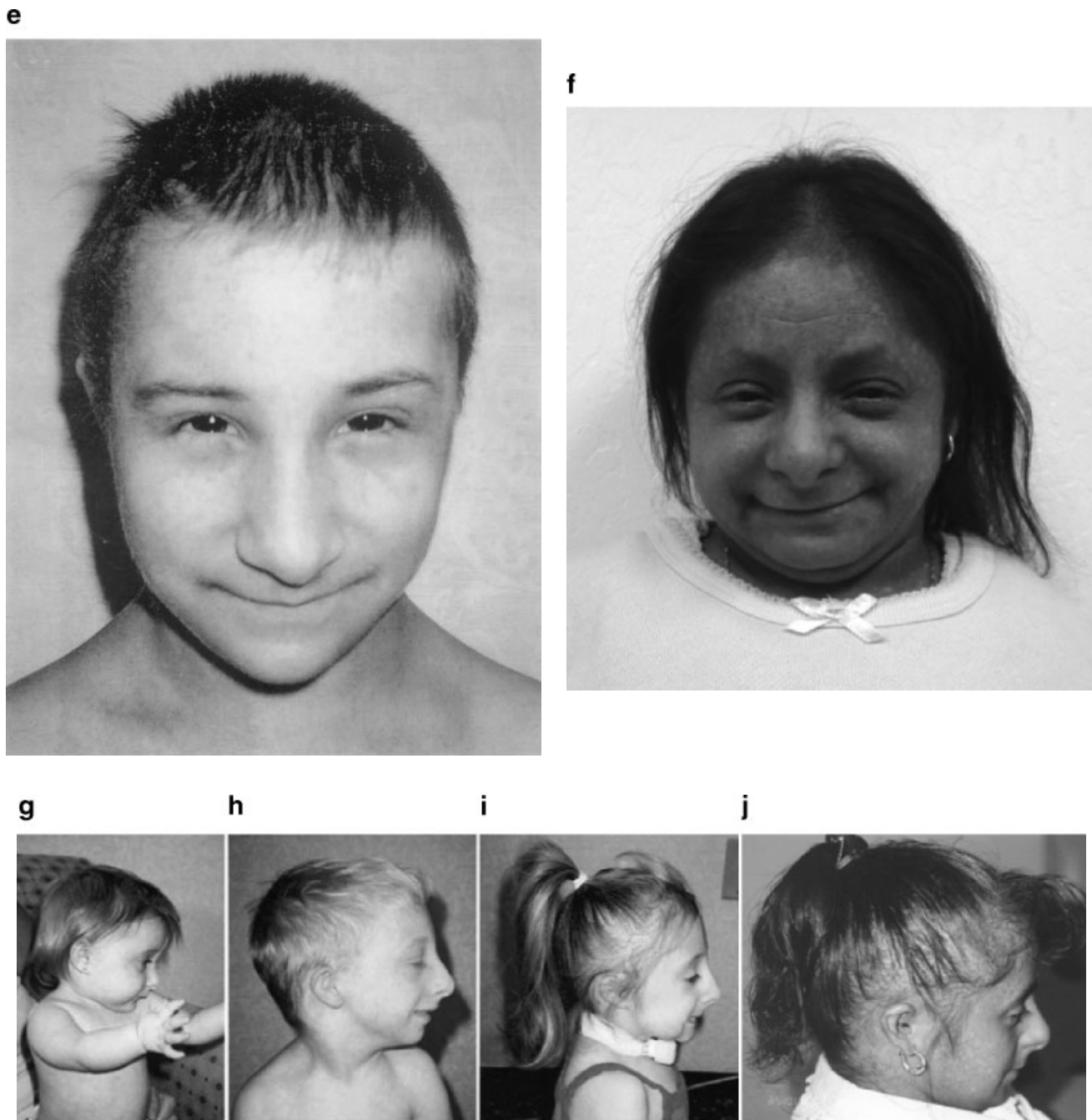


Fig. 9. (Continued)

children's diminutive size. Many children also have esotropia and astigmatism. Two affected individuals have had abnormal retinal pigmentation; one has a macular scar that could have been a vascular accident, and one has retinal-vascular changes. One child showed cupped discs and increased intraocular pressure during the second year of life possibly related to craniosynostosis. If cataracts are present, the syndrome described by Toriello et al. [1986] should be considered.

With aging the eyes, may become sunken giving the appearance of premature aging. The eyebrows often become sparse.

Teeth. Teeth are small (Fig. 10). They may appear small for size or in proportion, but never large. The primary teeth are small for age, but may appear normal in size with relationship to the mouth. Most often, there is increased space between the teeth. Often the teeth are mottled with deficient enamel. If there are secondary teeth, they may be quite small and



Fig. 10. Thirteen year old sister and 9 year old brother. Note missing secondary teeth, small teeth, space between the teeth, and the difference between the siblings.

dysplastic and may have mottled or hypoplastic enamel. The roots are often hypoplastic or even absent (Fig. 11). Not infrequently affected individuals have some relatively normal size and shape teeth next to very small and dysplastic teeth in both the primary and secondary dentition. Some children have some extremely small primary teeth that appear to be sharp little spikes. There is a broad range with regard to how severely the teeth are affected even within the same family. Since the permanent teeth are forming during the last trimester of pregnancy and first year of life, nutrition and growth during those periods may have some effect on the eventual size and appearance of the teeth. Most affected children are missing some permanent teeth and some children are missing some primary teeth. The oldest affected individual lost all her teeth in her 20s.

Cervenka et al. reported affected brothers in 1979, Tsuchiya et al. reported affected brothers in 1981, and Lin et al. reported affected brothers in 1995 as Seckel syndrome with microdontia. They all have similar clinical and dental findings and may have MOPD II, but the affected males are relatively tall with fairly severe mental retardation. Since all these cases are males, they may represent an X-linked form of MOPD which is milder. These cases all had reduced size of roots and hypoplastic alveolar processes with severe microdontia. There were uncalcified areas in the dentin and a reduced number of cells in the dental pulp in Tsuchiya's report [1981]. There is insufficient information to be clear whether they represent a distinct entity. By contrast, Kantaputra [2002] publication

claims to represent a new entity, but seems quite typical for MOPD II.

Ears. The ears may be simple or mildly dysplastic and are usually missing the lobule (Fig. 9). They may appear low set, or posteriorly angular, or even occasionally be prominent. The ears are usually not small for the head size, but will measure small for age. If the ears are disproportionately small, Meier-Gorlin syndrome should be considered. The ears in MOPD II do not appear large as they may in other types of microcephaly.

Many MOPD II affected children suffer from recurrent otitis which requires fairly vigorous therapy during the first few years of life to avoid permanent damage. Many MOPD II children, particularly girls, have needed hearing aids in childhood. They usually have been described as having a neuroconductive deficiency, although one child developed deafness related to high fevers.

Tracheal and Pulmonary Function

Many children have fairly severe respiratory problems in the newborn period, but have grown out of them. Four males have had tracheal (subglottic) stenosis sufficiently severe to be a problem with regard to breathing in infancy and two girls have required permanent tracheostomy. One girl had a vocal cord web and laryngomalacia. One boy who had multiple anomalies also had a misplaced upper lobe bronchus. In early childhood, URIs occur frequently, breathing can be labored and require hospitalization. Many children have recurrent URIs and pneumonia during the first few years of life suggesting a predisposition to infections, or that a mechanical problem may be present. With growth, the relative small tracheal size and pulmonary capacity usually improve. The chest often has an increased AP diameter and there may be mild pectus carinatum or excavatum. Pulmonary function is almost always said to be normal if measured (albeit difficult to measure). The development of scoliosis can threaten respiratory capacity. Decreased numbers of ribs (i.e., 11) have been seen in two males and one female.

Voice

Almost all of the affected children have a relatively high, squeaky, nasal voice. This is probably related to the small, narrow larynx and trachea, but it is so characteristic as to be helpful in making a diagnosis. At puberty, the voice may lower. A high, squeaky voice can also be seen in Meier-Gorlin, MOPD I, MOPD III, and Buebel syndromes.

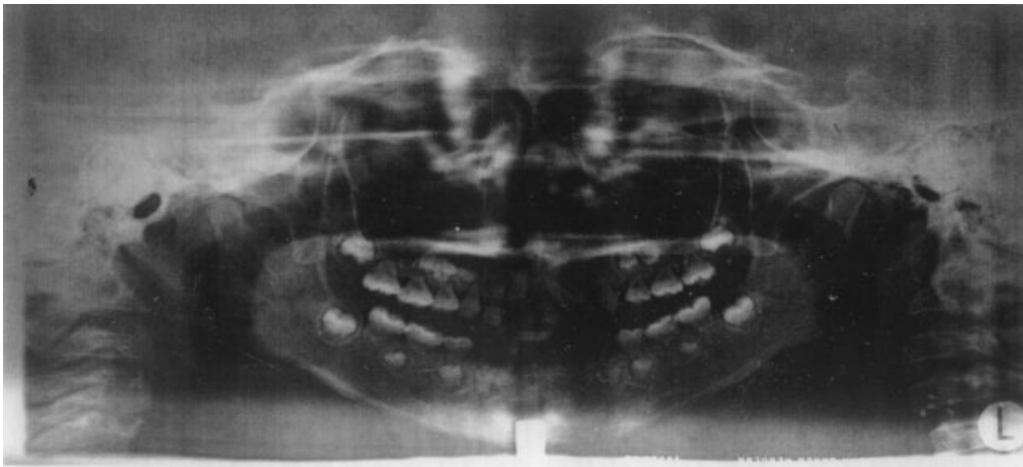


Fig. 11. Panorex demonstrating missing secondary teeth, hypoplastic roots, extremely small teeth, and dysplastic teeth.

Orthopedic Problems

In general, the bones are thin with progressive widening of the metaphyses of the long bones. The facial bones are small. There is usually delayed bone age in spite of the fact that dental maturation is early. Fusion of epiphyses, and puberty, may occur at an early age. This suggests that the generalized bony dysplasia seen in MOPD II affect the epiphyses as well as the metaphyses. The degree of severity of involvement of the bones may vary greatly, even within a family.

The hands are relatively short with tapering fingers in young children (Fig. 8b). The hands appear broad, and often have single creases or a decreased number of creases. There may be some puffiness of the dorsum in young individuals. With aging, the hands become more striking and disproportionately short and broad. They develop many creases and the skin of the hands is often quite dry. The knuckles become broad. Clinodactyly of the fifth finger is usually present and occasionally there is the fusion of the phalanges in the fifth finger with a single flexion crease.

The forearm may be slightly short at birth, but during childhood the span becomes progressively disproportionately shorter compared to height (Fig. 8b). With aging, the distal radius and ulna develop wide metaphyses, bow, and become quite dysplastic before fusing their epiphyses. Affected individuals often develop a rather knobby wrist joint with ulnar deviation. The radial head often dislocates, giving a knobby elbow with limited range of motion (Fig. 8b). Flexion contractures of the elbow may develop. This dislocation of the elbow is usually not present at birth, but occurs over the first 5–10 years. The joints progressively develop hyperextensibility so that the fingers, hips, knees, ankles, and feet may sublux. In some older individuals the knees may dislocate laterally and require bracing (Fig. 8b).

Progressive disproportion occurs over time in most children with relative shortening of distal limbs giving an appearance of relative shortening (although of course the hands and feet are also small). The knees become more prominent and may dislocate laterally because of loose lateral ligaments. The patellae are present. The feet become relatively smaller and broader with age. They may, as in the hands, show puffiness in young children. There may be a wide space between the big toe and second toe.

The hips may be dislocated at birth, but almost always there is mild coxa vara at an early age which progresses in severity, often requiring surgery (Fig. 12). The femoral head epiphysis seems to slip down along the shaft giving the appearance of a proximal femoral epiphysiolysis on X-ray.

With walking many MOPD II individuals develop marked lumbar lordosis. Scoliosis may occur, particularly in girls and particularly in the lumbar area in late childhood (as early as 9 years) or at puberty. It can progress very rapidly and needs to be watched carefully. Many individuals have required bracing or surgery for scoliosis, which again must be customized because of the very diminutive size.

Characteristic Radiographic Changes

In the newborn period, little is obviously unusual in the X-rays except perhaps the pelvis which is high and narrow with small iliac wings and flat acetabulum. It may be necessary to observe the radiographic changes over many years to appreciate the typical changes. The long bones are gracile and overtubulated (Fig. 13). Ossification is delayed so the bone age always appears to be delayed. As the epiphyses begin to manifest, the femoral head is small and hypoplastic with a short neck and, gradually, severe coxa vara develops, such that between the age of 3 and 8 epiphysis of the femoral head may occur. The distal femur which seems normal initially begins to



Fig. 12. Pelvis showing coxa vara.

develop a metaphyseal flare. As the distal femur epiphysis ossifies, it becomes triangular and the distal femoral metaphyses develop a V-shape. The ilia are high and narrow. There are narrow ischial and pubic bones. At the elbow, the proximal radius is not well seated and usually dislocates.

The distal radius and ulna develop metaphyseal flaring, undergrowth, and often bow significantly towards each other. The mesomelic segment becomes relatively short (Fig. 14). In the wrist, the delayed ossification is seen and some carpals may fuse. All of the epiphyses tend to be irregular, particularly in the hand where ivory epiphyses may be seen (Fig. 15). Pseudoepiphyses of the metacarpals are often seen and the first and fifth metacarpals are often short. The distal phalanges are often hypoplastic.

The vertebrae may be mildly flat in young children. Foreshortening of vertebral bodies develops in older children. The clavicles may appear long and thin. The bony changes may not be striking, but are usually present by age 10. The vertebrae are often delayed in their maturation (Fig. 16), but are relatively proportionate. Hypoplastic or absent ribs may be seen (Fig. 16).

The skull is relatively normally proportionate (Fig. 17) although the facial bones may appear small and the sella may appear large.



Fig. 13. Arm showing thin long bones.

Cardiovascular

The heart is usually normal, although one affected male had a bicuspid aortic valve, one female had an atrial septal defect (ASD), two females had PDAs, and one female died with a myocarditis and myocardial infarct. Blood pressure is normal.

Genitourinary

Males often have cryptorchidism. The testes are small for age, and may even appear small for body size. They do enlarge at puberty, but only minimally. One male had hypospadias. Most have a penis that is small for age but in proportion to their bodies; however, at least one has been described as small. Many males have had inguinal hernias that require repair.

Female external genitalia usually appear normal, although the clitoris may appear large if the labia are underdeveloped. As mentioned above, in females with MOPD II, precocious puberty is frequent.

Renal abnormalities have been seen both with regard to the position of the kidney and to underdevelopment of the kidneys. One male had unilateral cystic dysplasia of the kidney, another female had a unilateral hypoplastic kidney, another female had a small kidney, and one male had a dysplastic horseshoe kidney. Urinary tract infections have been reported in two



Fig. 14. Leg distal femur with flare and short middle segment.

other females and nephrolithiasis in one male with hydroxylapatite stones.

Dermatological Changes

Hair tends to be fine and mildly sparse such that the scalp can frequently be seen through the hair. The eyebrows tend to be thin. The skin is dry. In infants, mottling is seen frequently on the limbs and occasionally on the trunk. Multiple creases develop on the hands and feet with aging.

An unusual type of pigmentation is present in all of the affected individuals and seems to be progressive. In the newborn period, children usually have no unusual pigmentation, however, over the first 2 years multiple café au lait spots develop. Many children also develop freckling. By 5 years of age, most children have developed increased dark

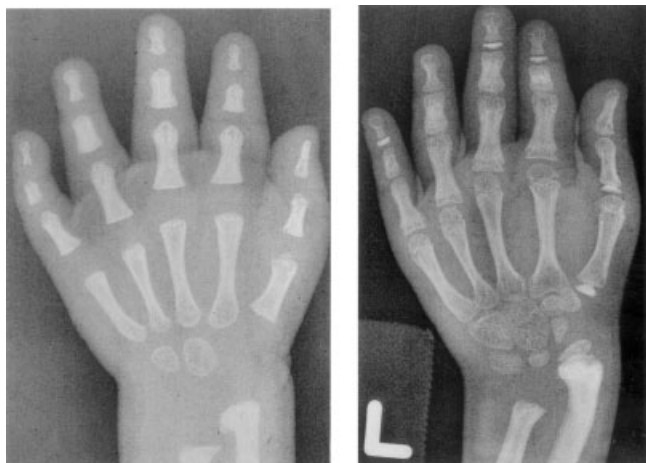


Fig. 15. Hand at 2 and 9 years in same child. Note ivory epiphyses and short ulna.

pigmentation around the neck, on the trunk and in the axilla. This is not acanthosis, since it does not thicken or become velvety, but certainly represents an increase in pigmentation for the individuals depending on their ethnic background. If true acanthosis is present, the syndrome summarized by Salerno et al. [2003] should be considered. This pigment increases with sun exposure, growth hormone therapy, and in areas of trauma. By puberty, all individuals have darkening and then they begin to develop areas of thickening and eczema-like skin changes which become mottled with patchy loss of pigment. The areas of depigmentation may arise at an earlier age particularly in sun exposed areas. By late teens, diffuse keratosis maybe seen with thinning of the skin. Poikiloderma usually develops in sun exposed areas. Sacral dimples have been present in four girls.

Immunologic and Hematologic Features

Several affected individuals have had anemia, but only one (who had no evidence of Fanconi anemia) was severe enough to require bone marrow transplantation. Many individuals have had recurrent infections in infancy and early childhood,

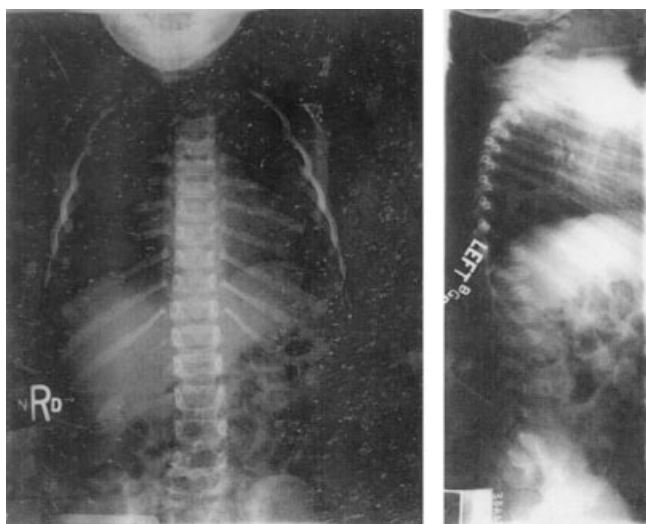


Fig. 16. Lateral chest 2 years, AP chest at 4 years. Note delayed maturity, mild flattening, hypoplastic rib.



Fig. 17. Skull showing inward markings on inner table and relatively large sella.

suggesting an increased susceptibility to infection or an abnormal immune response although various laboratory investigations have not demonstrated any constant abnormality. One girl developed glomerulonephritis requiring a kidney transplant.

Laboratory Studies

Numerous laboratory studies have been done and, for practical purposes, they are all normal including chromosomes, T4, insulin, growth hormone, somatomedin, TSH, LH, FSH, urinary hormone excretion, CBC, glucose, electrolytes, urea, and urinalysis. Occasional anemia is seen perhaps due to blood drawing, still it usually resolves. EEG and EKGs are usually normal, although three individuals have had apparent seizures.

Causes of Death

There have been 11 known deaths (3 males, 8 females) among the 58 cases that were well-studied. Ages at death were 10 months, 6 months, 4 years, 5 years, 6 years, 10 years, 11 years, 13 years, 19 years, 21 years, and 25 years. Not all had autopsies, but it is thought that three were related to sepsis (ages 16 months, 5 years, and 11 years), one gastrointestinal disease and dehydration (10 months), one related to nephrotic syndrome and renal failure with renal transplantation and subsequent cytomegalovirus infection (4 years), one vomiting with cardiac arrest (6 years), one related to cardiomyopathy (10 years), and four were thought to be due to the rupture of CNS aneurysm (13, 19, 21, and 25 years). There were also four deaths in sibs where there was insufficient information to determine cause of death. These include the death of a newborn male, two terminations of pregnancy and one affected miscarriage. The oldest known living affected individual is 37 years old: a woman who is postmenopausal and wizened in appearance with patchy skin pigmentation. She is pleasant, interactive, and engaging.

Inheritance

Combining the 27 reported cases and our 31 unpublished, affected individuals, there are now 53 families with 58

individuals about whom there is sufficient information to include in our description of natural history. There are 22 males and 36 females suggesting a skewed sex ratio, since a little less than 2/5 of the cases are males and 3/5 are females. Nine of the families are consanguineous and there are eight sets of affected siblings; however, details about both siblings to include in this report are only available from five of the families all of which are male–female pairs. Marked intrafamilial variability has been noted in phenotypic features, again making it difficult to define the limits of the condition. It is also difficult to determine whether certain features are more likely to be seen together and whether they can be influenced by environment (e.g., the specific mutation, the age at delivery, early nutrition, etc.).

It appears that MOPD II has an autosomal recessive pattern of inheritance since consanguinity has been observed, parents are unaffected and of normal stature, and both males and females are affected. The number of females appear to be greater, but families do not report an increase in miscarriages or deaths of males. Some ethnic groups (Middle East, France, Japan, and Mexico) may be reporting more affected individuals than expected and so may have an increased carrier frequency suggesting a possible founder effect and even carrier advantage. MOPD II, which was until recently thought to be very rare, may not really be rare.

Although studies to identify the responsible gene have been initiated, thus far it has not been identified. Possibly different mutations of a single gene may also produce some of the variants not included in this report [Tsuchiya et al., 1981; Sugio et al., 1993; Lin et al., 1995; Buebel et al., 1996; Bongers et al., 2001]. In addition, various allele combinations could produce the spectrum of features observed. Possibly, small chromosomal deletions in the region of the responsible gene together with a mutant allele on the other chromosome may produce some of the more complex anomalies seen in some affected individuals (e.g., renal anomalies, abnormal number of ribs, severe mental retardation, etc.). And, finally, the responsible gene may be part of a pathway along which different mutant genes are responsible for producing the spectrum of disorders.

Natural History

Medically speaking, in addition to severe intrauterine and postnatal growth retardation, progressive changes do occur. Skeletal changes include increasing ligamentous laxity with dislocations, metaphyseal widening and irregularities, and low thoracic scoliosis. Affected individuals are often farsighted apparently due to failure of the eyeball to grow in length. Abnormalities of dentition include very small teeth with dysplastic enamel and roots, together with missing, primary and secondary teeth. The role of postnatal nutrition in dental growth is not clear. A type of arterial anomaly forms by out-pocketing of the arteries which leads to multiple aneurysms in some individuals that may lead to intracranial bleeding and strokes. Increased pigment in the skin is seen during childhood. All of these features suggest the body of the affected individual has a block to normal tissue growth and various mechanisms are put into action to try to stimulate growth within the body, leading to excess output in some areas (pigment, vessel growth), but failure to accomplish normal somatic growth. The mechanisms to sense and maintain bodily proportion, however, seem to be intact.

Most of these children are born prematurely and about half of the births have been induced because of abnormal prenatal stress tests. It would appear that the babies “get into trouble” in the last trimester of pregnancy. They have quite small placentas even for their size. It is not clear whether affected infants do better by being delivered early and whether delivering early allows better nutrition. Clearly nutritional and

respiratory supports are frequently needed in the newborn period.

Concerns at the time of birth include hypoglycemia. Most MOPD II children have some respiratory distress at the time of birth. This may well relate to the very small trachea and larynx at birth. Most affected infants have required intubation and ventilation for some period of time. Respiratory support may be required for several months. Most affected infants have trouble with bottle-feeding. It is not clear whether this is related to the problems around respiration or to poor suck. Many infants have been tube fed and required gastrotomies.

Early in life sleeping difficulties are frequently reported including frequent waking. The affected babies frequently need multiple small feedings though the night. When the children do sleep, they tend to snore or “hum” while they breathe.

Respiratory problems may be severe. Most children have recurrent URIs, but may also have recurrent pneumonias. Several have reported the development of allergies, which may aggravate the respiratory problems.

The body proportions become more disproportionate with the middle segment of the limbs becoming proportionately shortened in most children. The ligaments around the joints become hyperextensible and may become overextended leading to frequent dislocations over time. The head growth is even less after birth than is body growth. As mentioned above, growth hormone therapy does not seem beneficial and possibly may lead to complications.

Scoliosis may develop before puberty but it seems to be most closely related to the pubertal growth spurt and may progress very rapidly.

Differential Diagnosis

The differential diagnosis for MOPD II is complex. There are many causes of IUGR, but very few of such severity. Most of the unusual features (squeaky voice, small teeth, outgoing personality, etc.) can be seen in other syndromes. The distinctive unusual pigment and bone dysplasia develop over time. Syndromes with IUGR include those with large heads, those with diagnostic laboratory tests, and those with specific physical features, such as:

- Russell–Silver syndrome, 3-M syndrome [Hennekam et al., 1987], SHORT syndrome [Sorge et al., 1996], and Floating Harbor syndrome all have IUGR, but have normal for age (therefore disproportionately large) head sizes.
- Antley–Bixler syndrome, Cornelia de Lange syndrome, and Dubowitz syndrome have IUGR, microcephaly, characteristic facies, specific anomalies, and unique natural histories. They also tend to be much larger at birth.
- Goldblatt et al. [1991] reported a boy with a distinguishable spondylometaphyseal dysplasia with short stature, short middle segment, hyperextensibility, and mottled teeth.
- Fanconi syndrome, Bloom syndrome, and ataxia telangiectasia are larger at birth and have specific laboratory diagnostic tests that can be performed to make the diagnosis.
- Seckel syndrome, MOPD I, and MOPD III all have moderate IUGR and have distinctive features that allow them to be distinguished from MOPD II (i.e., Seckel syndrome has developmental delay and severe mental retardation, severe microcephaly at birth, no bony dysplasia; MOPD I has significant CNS malformations, sparse hair, dry skin, long clavicles, flattened vertebrae, under modeled long bones, and wide proximal femur; MOPD III has severe mental retardation and developmental delay, severe microcephaly, enlarged sella, narrow face, large pointed nose, and hypoplastic pelvis).

There have been many other similar conditions described which can be separated from MOPD II.

- Meier–Gorlin has moderate IUGR with average birth weight around 1,800 g at term, absent patellae and very small ears. Females may fail to develop breast tissue at puberty. A range of intelligence is seen.
- The syndrome described by Toriello et al. [1986] has moderate IUGR within the range of birth weights 1,500–1,700 g, relatively normal facies and nose, moderate microcephaly, and mental retardation, no bony dysplasia, but generalized delay of ossification, immune deficiency, and cataracts.
- The syndrome described by Saul and Wilson [1990] and Hersh et al. [1994] includes birth weights around or just below the 3rd centile for gestational age, characteristic facies with frontal bossing, depression over the metopic suture, mid-face hypoplasia, prominent eyes, and brachydactyly. Over-tubulated bones, coning and sclerosis of epiphyses, hypoplasia of the odontoid, irregular vertebral bodies and plates, and coxa valga of hips are also seen.
- The syndrome described by Hurst et al. [1988] in two boys includes external ear anomalies, small mandible, microstomia, microcephaly, contractures, a mild skeletal dysplasia, and birth weight around the 3rd centile.
- The syndrome described by Bangstad et al. [1989] and Salerno et al. [2003] as well as by Scott [1969] and in Kogut and Sensenbrenner [1975] in males (two sets of brothers) with moderately severe IUGR, microcephaly, craniosynostosis, moderately severe post uterine growth retardation, deafness, deep set eyes, cryptorchidism, truncal obesity, and acanthosis nigricans, small teeth, prognathism, dislocated radial heads without generalized skeletal dysplasia, however, tall vertebrae, moderate mental retardation, hypothyroidism, insulin resistance, hypoparathyroidism.
- The syndrome described by Buebel et al. [1996] (Case 1) in which there is moderate IUGR, relative macrocephaly at birth, syndactyly of toes, severe retromicrognathia, severe microstomia, submucous cleft, small palpebral fissures, partial ptosis, lack of a high bridge of the nose, and scoliosis probably represents a different disorder. Sugio et al. [1993] (Case 2) may have the same condition as Buebel's Case 1.
- The male cases (three sets of brothers) reported by Cervenka et al. [1979], Tsuchiya et al. [1981], and Lin et al. [1995] are larger at birth and after puberty than typical MOPD II cases. They seem to have more mental retardation as well.

Until the gene(s) responsible for MOPD II is found, it is not possible to distinguish whether some of these conditions are allelic or differential expression of the same gene reflecting the differences in mutations. The last two disorders would be most likely to be allelic. Nevertheless, by using a narrow definition of MOPD II, much has been learned about the natural history, inheritance pattern, and specific phenotype from these 58 cases that should allow recognition and preventive therapies.

Faivre et al. [2002] published linkage for Seckel syndrome and most recently O'Driscoll et al. [2003] found at least one of the responsible genes for Seckel syndrome. However, linkage for MOPD II has not been established.

SUMMARY

This disorder clearly has an autosomal recessive pattern of inheritance. The frequency may be increased among some ethnic groups, but is clearly more common than previously appreciated. It is characterized by very severe IUGR and postnatal growth. Individuals with MOPD II are among the very smallest human beings at maturity. Their pleasant,

outgoing personality, high-pitched nasal voice, and distinctive facial features make them very recognizable. Life expectancy is decreased, but individuals are known to live into their 30s. Many complications arise, but most can be handled by adapting modern medical techniques to their diminutive size. The responsible gene has not been identified, but will surely provide insight into an important pathway for the control of the growth of many different tissues. Normal response to growth stimulating hormones is lacking, and yet relative proportions are maintained surprisingly well. Disharmonic bone growth, CNS growth, CNS vascular growth, and pigmentary response suggest some intrinsic imbalance or lack of normal responsiveness by many tissues.

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