

Clinical Report

Majewski Osteodysplastic Primordial Dwarfism Type II (MOPD II) Complicated by Stroke: Clinical Report and Review of Cerebral Vascular Anomalies

Francesco Brancati,^{1,2,3} Marco Castori,^{2,3} Rita Mingarelli,³ and Bruno Dallapiccola^{2,3*}

¹Department of Biological Sciences, University "G. D'Annunzio", Chieti, Italy

²Department of Experimental Medicine and Pathology, University "La Sapienza", Rome, Italy

³CSS Hospital, IRCCS, San Giovanni Rotondo and CSS Mendel Institute, Rome, Italy

We report on a 29/12-year-old boy with disproportionate short stature, microcephaly, subtle craniofacial dysmorphisms, and generalized skeletal dysplasia, who developed a left hemiparesis. Brain neuroimaging disclosed a complex cerebral vascular anomaly (CVA) with stenosis of the right anterior cerebral artery and telangiectatic collateral vessels supplying the cerebral cortex, consistent with moyamoya disease. Based on clinical and skeletal features, a diagnosis of Majewski osteodysplastic primordial dwarfism type II (MOPD II) was established. Review of 16 published patients with CVA affected by either Seckel syndrome or MOPD II suggested that CVA is preferentially associated to the latter subtype affecting about 1/4 of the patients.

© 2005 Wiley-Liss, Inc.

KEY WORDS: MPD; MOPD; Seckel; cerebral; vascular; stroke

INTRODUCTION

Microcephalic primordial dwarfisms (MPDs) are autosomal recessive disorders characterized by pre- and post-natal growth retardation, microcephaly, and distinct facial gestalt with prominent beaked nose, receding forehead, and micrognathia [Majewski and Goecke, 1982; Majewski et al., 1982a,b]. MPDs comprise (1) Seckel syndrome, with no signs of skeletal dysplasia, and (2) Majewski (also termed microcephalic) osteodysplastic primordial dwarfisms (MOPDs), which are constitutional bone disorders [Hall, 2002; Hall et al., 2004]. Three types of MOPDs (I–III) have been delineated both on clinical and skeletal features. Type II MOPD is the most common type with more than 60 patients reported so far [Hall et al., 2004; Kannu et al., 2004; Young et al., 2004; Ozawa et al., 2005]. Characteristic features of MOPD II are peculiar growth pattern with very severe IUGR and adult height below 110 cm, neonatal proportioned head size later progressing to microcephaly, absent or mild mental retardation, and typical bone dysplasia. Abnormal dentition,

skin pigmentation, and obesity may also be observed together with cerebral vascular anomalies (CVA) [Hall et al., 2004].

CVA are life threatening complications reported in patients diagnosed with either MOPD II or, rarely, Seckel syndrome. Observed vascular changes include moyamoya disease, tortuous vessels, multiple intracranial aneurysms, and polyarteritis nodosa (PAN) with irregular narrowing of cerebral arteries [D'Angelo et al., 1998; Sorof et al., 1999; Di Bartolomeo et al., 2003; Nishimura et al., 2003; Hall et al., 2004; Kannu et al., 2004; Kutlu et al., 2004; Young et al., 2004]. The natural history and pathogenesis of such complications are still unclear, although a systemic vascular disease affecting both intracranial and extracranial arteries could be the underlying mechanism, as reported in otherwise healthy children with moyamoya disease [Aoyagi et al., 1996]. The importance of a timely diagnosis and management of CVA in MOPD II patients has been recently emphasized as they can be a major cause of stroke and early death [Hall et al., 2004].

Here, we describe a novel MOPD II boy affected by moyamoya disease complicated by stroke. Review of published MPD patients with CVA, outlined a rather wide spectrum of anomalies and suggested a distinct association with a MPD subtype.

CLINICAL REPORT

This is a 29⁹/₁₂-year-old boy, first child of healthy, non-consanguineous parents. The mother was a 29-year-old and the father 33. Pregnancy was complicated by intrauterine growth retardation, first noticed at 17 weeks. Prenatal infections were tested negative and no teratogenic exposure was reported. The baby was born by caesarean in the 31st gestational week because of poor growth with weight 752 g, length 32 cm, and OFC 23.5 cm (all below the 3rd centile). At birth, growth retardation was symmetrical and cutis marmorata observed over the trunk and limbs. Cranial fontanelles were closed. Reported dysmorphisms included prominent nose, small mouth, micrognathia and bilateral simian crease. Persistent ductus arteriosus resolved spontaneously. Bilateral cryptorchidism was also present.

Skeletal X-rays, performed at 6 and 18 months, showed a marked bone age retardation (corresponding to the neonatal period in both measurements), without any other abnormality but brachydactyly and precocious closure of the cranial sutures. Psychomotor development was mildly retarded. He rolled over at age 9 months and sat alone at 10 months, stood with support at 1½ year(s) and walked alone at 2³/₁₂. A high-pitched voice was recorded. At age 2 years, he developed a sudden-onset left hemiparesis and presented to the emergency room. Blood pressure was 100/40 mmHg. A brain CT scan revealed a right anterior cerebral ischemic lesion while on magnetic resonance angiography (MRA) a marked stenosis of the right anterior cerebral artery and associated telangiectatic collateral vessels, which supply the cortex (moyamoya disease)

Grant sponsor: Italian Ministry of Health.

*Correspondence to: Bruno Dallapiccola, University of Rome "La Sapienza", C.S.S. Mendel Institute, Viale Regina Margherita, 261, I-00198 Rome, Italy. E-mail: dallapiccola@css-mendel.it

Received 19 May 2005; Accepted 31 August 2005

DOI 10.1002/ajmg.a.31009

© 2005 Wiley-Liss, Inc.



Fig. 1. Frontal (a) and lateral (b) facial appearance of the patient with large eyes, sparse eyebrows, hypoplastic nasal tip and thin alae nasi, prominent cheeks, attached ear lobules and micrognathia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

were present. Results of blood tests for thyroid hormones, IGF-1, and endocrinological test for growth hormone after clonidine load were all normal. Karyotype was 46,XY at standard level. At this time, the diagnosis of Seckel syndrome was suggested.

At time of examination at age 2⁹/₁₂ years, he was a friendly boy who pronounced simple words with a high-pitched voice. He was able to walk with a tendency to falling due to residual left weakness. He did not present other neurological abnormalities. His weight was 6,200 g, head circumference 41.5 cm, and length 65.5 cm (all values below the 3rd centile). Disproportionate short limbs with respect to the trunk and brachydactyly were evident. Craniofacial characteristics included micro-brachycephaly, prominent eyes and cheeks, broad nasal root with wide nasal bridge, hypoplastic alae nasi and nostrils, microstomia and receding chin (Fig. 1).



Fig. 2. Cutis marmorata over the trunk and thighs. Note cryptorchidism. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The teeth were small and reduced in number with signs of enamel hypoplasia. Skin examination disclosed generalized cutis marmorata over the trunk and limbs (Fig. 2). Re-evaluation of the skeletal exams (performed at age 6 and 18 months) showed long bones overtubulation with shortening of the middle segments of upper and lower limbs, brachytelephalangia I–V and brachymesophalangia II–V on hands and feet, clinodactylous fifth fingers, proximally placed thumbs, moderately high lumbar vertebrae, narrow and high iliac wings, narrow ischial and pubic bones, triangular distal femoral epiphyses, and metaphyseal flaring particularly involving the distal femoral metaphyses which assumes a “delta” appearance (Fig. 3).

DISCUSSION

This patient is affected by MOPD II phenotype based on clinical and radiographic findings (Figs. 1 and 3). The diagnostic criteria of MOPD II were only recently outlined [Hall et al., 2004], while in the past, there had been some confusion



Fig. 3. Skeletal survey of the patient at 18 months shows absent carpal ossification centers, proximally placed thumb and clinodactylous fifth finger (a), hypo/aplastic middle and distal phalanges (a, b), mesomelic shortening of the limbs (c), overtubulated long bones (a–c), “delta”-shaped distal femoral metaphysis and triangular distal epiphysis (d). Pelvis (at 6 months) showing high iliac wings, narrow ischia, and pubis (e).

TABLE I. Patients With MPDs and CVA

Diagnosis	Seckel syndrome				MOPD II				
Reference	D'Angelo et al. [1998]*	Sorof et al. [1999]	Di Bartolomeo et al. [2003]	Kutlu et al. [2004]	Nishimura et al. [2003]*	Kannu et al. [2004]	Hall et al. [2004]*	Young et al. [2004]	Present case
Sex	Female	Male	Male	Male	Male	Female	Four males and five females*	Female	Male
Age	17 y	19 y	10 y	9 y	7 y	7 y and 3 m	Overgrowth of the CNS vessels (prenatal 25 y)	6 y and 9 m	2 y and 9 m
CVA (age at diagnosis)	Multiple aneurysms, elongated and twisted vessels (11 y)	Multiple aneurysms (19 y)	Multiple aneurysms and teleangiectases (10 y)	Irregular narrowing of arteries in presence of PAN (9 y)	Moyamoya disease (4 y and 5 m)	Moyamoya disease (2 y and 11 m)	Overgrowth of the CNS vessels (prenatal 25 y)	Moyamoya disease (2 y and 6 m)	Moyamoya disease (2 y)
Other vascular complications	DC; H	DC; H	DC; H	DC; H; mesenteric/renal arteries aneurysms	CM	CM	CM	CM	CM
Outcome	Hemiparesis	Death	Disphasia	Hemiparesis	Hemiparesis	Hemiparesis and headaches	Intrauterine vascular accident; emiparesis; death	Disability, aphasia, seizures	Hemiparesis
Skeletal survey	a	Evidence of osteodysplasia, b	CV, MSL (with BR), NIIP, TH	Unavailable	CV, BD, MF, OLB	BD, CV, MF, MSL, NIIP, TFE	Unavailable	BD, MF, NIIP	BD, MF, MSL, NIIP, OLB, TFE
Suggested diagnosis	MOPD II	Unclassified MOPD	MOPD II	Unclassified MPD					

BD, brachydactyly with brachymeseso- or brachytelemeso-phalanges; BR, bowed radius; CM, cutis marmorata; CV, coxa vara; DC, dilated cardiomyopathy; H, hypertension; MF, metaphyseal flaring of the knee with delta-shaped distal femoral metaphyses; MSL, mesomelic shortening of the limbs; NIIP, narrow iliac, ischial and pubic bones; OLB, overubulated long bones; PAN, polyarteritis nodosa; TFE, triangular distal femoral epiphyses; TH, trident hand; MPDs, microcephalic primordial dwarfisms; CVA, cerebral vascular anomaly, y, year(s); m, month(s).

a: Reportedly abnormal in Hall et al. [2004] but data on skeletal abnormalities were unavailable, as also in (b) Sorof et al. [1999].

*Two out of eleven patients with CVA reviewed by Hall et al. [2004] are described apart in the table (see D'Angelo et al. [1998] and Nishimura et al. [2003]).

between MOPD II and other MPDs (i.e., Seckel syndrome). The first patients with MOPD II were in fact diagnosed retrospectively by Majewski and Goecke [1982] in two patients referred to as Seckel syndrome [Brizard et al., 1973; Anoussakis et al., 1974]. Moreover, one of the MOPD II patients reviewed by Hall et al. [2004] was previously diagnosed with Seckel syndrome. Interestingly, this patient had multiple intracranial aneurysms with elongated and twisted vessels [D'Angelo et al., 1998]. This observation prompted us to review published patients with CVA having received a diagnosis of any type of MPD. Di Bartolomeo et al. [2003] diagnosed Seckel syndrome in a patient with sparse scalp hair, generalized skeletal dysplasia (i.e., high and narrow iliac wings, narrow ischial, and pubic bones, bilateral coxa vara, proximal femoral epiphysiolysis, bowed radius, ulnar deviation of hand and wrist, and trident hand) and facial gestalt consistent with MOPD II. Also this patient had chronic severe hypertension and multiple intracranial aneurysms with telangiectatic vessels. A similar CVA was diagnosed in an additional Seckel syndrome patient with "evidence of osteodysplasia," although no radiographs were shown [Sorof et al., 1999]. Based on published diagnostic criteria, there was insufficient clinical information to allow reasonable classification of the MOPD in this patient [Majewski et al., 1982a; Hall et al., 2004]. Finally, no skeletal survey was available in the Seckel syndrome patient by Kutlu et al. [2004], who had multiple CVAs secondary to PAN. Thus, in two patients a diagnosis of MOPD II was suggested, while two cases could not be classified. The clinical characteristics of three further patients diagnosed with MOPD II who had CVAs, added to the list of nine individuals reported by Hall et al. [2004], are summarized in Table I. We are unaware of patients with either MOPD I or III presenting with CVAs. Hence, including our patient, a total number of 17 cases of MPD with CVA have been reported (Table I).

Observed CVAs included multiple aneurysms or moyamoya disease, invariably complicated by neurological impairment ranging from residual dysphasia to sudden death. Patients with moyamoya disease show an earlier age at onset of these complications compared to the group with intracranial aneurysms although, this latter subset of subjects had a worse prognosis due to chronic severe hypertension and dilatative cardiomyopathy [Sorof et al., 1999; Di Bartolomeo et al., 2003]. Chronic hypertension has not been previously described in MOPD II. Despite its current apparent rarity and given its significant morbidity, blood pressure monitoring should become part of the regular surveillance of MOPD II patients, particularly in adolescence and adult life. Interestingly, in two patients (including ours) moyamoya disease was associated with cutis marmorata [Kannu et al., 2004]. Finally, one individual had PAN with abnormal CNS vessels [Kutlu et al., 2004]. It is still unclear whether PAN is part of the CVA spectrum associated with MPDs as this is the only reported patient showing extra CNS vascular involvement.

Overall, among these 17 patients, a final diagnosis of MOPD II was established in 15, while two had an unclassified MOPD. The prevalence of CVAs in MOPD II among a total of 62 published patients [Hall et al., 2004; Kannu et al., 2004; Young et al., 2004; Ozawa et al., 2005] was then calculated at 23.8% (15/63), including the present case.

In conclusion, present results strengthen CVAs as frequent, life threatening complications of MOPD type II, and highlight the importance of a timely CNS vascular imaging in the clinical management of these patients.

ACKNOWLEDGMENTS

This work was supported by funding from the Italian Ministry of Health grant "Ricerca Corrente 2005" and approved by the local ethic committee.

REFERENCES

- Anoussakis CH, Liakakos D, Zervos N, Karpathios TH. 1974. Les nanismes congénitaux avec dysmorphie: II. Le nanisme congénital à tête d'oiseau (type Virchow-Seckel). *Pediatric* 29:261–267.
- Aoyagi M, Fukai N, Yamamoto M, Nakagawa K, Matsushima Y, Yamamoto K. 1996. Early development of intimal thickening in superficial temporal arteries in patients with moyamoya disease. *Stroke* 27:1750–1754.
- Brizard J, Mimouni M, Seneze J, Thoyer-Rozat J. 1973. Sur un cas de nanisme extrême à début intra-utérin vraisemblablement du type Seckel. *Ann Pediatr* 20:655–660.
- D'Angelo VA, Ceddia AM, Zelante L, Florio FP. 1998. Multiple intracranial aneurysms in a patient with Seckel syndrome. *Childs Nerv Syst* 14:82–84.
- Di Bartolomeo R, Polidori G, Piastra M, Viola L, Zampino G, Chiaretti A. 2003. Malignant hypertension and cerebral haemorrhage in Seckel syndrome. *Eur J Pediatr* 162:860–862.
- Hall CM. 2002. International nosology and classification of constitutional disorders of bone (2001). *Am J Med Genet* 113:65–77.
- Hall JG, Flora C, Scott CI Jr, Pauli RM, Tanaka KI. 2004. Majewski osteodysplastic primordial dwarfism type II (MOPD II): Natural history and clinical findings. *Am J Med Genet Part A* 130:55–72.
- Kannu P, Kelly P, Aftimos S. 2004. Microcephalic osteodysplastic primordial dwarfism type II: A child with café au lait lesions, cutis marmorata, and moyamoya disease. *Am J Med Genet Part A* 128A:98–100.
- Kutlu R, Alkan A, Kutlu O, Yakinci C. 2004. Seckel syndrome with polyarteritis nodosa. *Indian Pediatr* 41:1158–1161.
- Majewski F, Goecke T. 1982. Studies of microcephalic primordial dwarfism I: Approach to a delineation of the Seckel syndrome. *Am J Med Genet* 12:7–21.
- Majewski F, Ranke M, Schinzel A. 1982a. Studies of microcephalic primordial dwarfism II: The osteodysplastic type II of primordial dwarfism. *Am J Med Genet* 12:23–35.
- Majewski F, Stoeckenius M, Kemperdick H. 1982b. Studies of microcephalic primordial dwarfism III: An intrauterine dwarf with platyspondyly and anomalies of pelvis and clavicles—osteodysplastic primordial dwarfism type III. *Am J Med Genet* 12:37–42.
- Nishimura G, Hasegawa T, Fujino M, Hori N, Tomita Y. 2003. Microcephalic osteodysplastic primordial short stature type II with café-au-lait spots and moyamoya disease. *Am J Med Genet Part A* 117:299–301.
- Ozawa H, Takayama C, Nishida A, Nagai T, Nishimura G, Higurashi M. 2005. Pachygyria in a girl with microcephalic osteodysplastic primordial short stature type II. *Brain Dev* 27:237–240.
- Sorof JM, Dow-Smith C, Moore PJ. 1999. Severe hypertensive sequelae in a child with Seckel syndrome (bird-like dwarfism). *Pediatr Nephrol* 13:343–346.
- Young ID, Barrow M, Hall CM. 2004. Microcephalic osteodysplastic primordial short stature type II with café-au-lait spots and moyamoya disease: Another patient. *Am J Med Genet* 127A:218–220.