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Original Article

# Screening for Cerebrovascular Disease in Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD II): An Evidence-Based Proposal

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ABSTRACT

Microcephalic osteodysplastic primordial dwarfism type II (OMIM 210720) is a rare autosomal recessive condition frequently associated with early-onset cerebrovascular disease. Presymptomatic detection and intervention could prevent the adverse consequences associated with this. We reviewed published cases of microcephalic osteodysplastic primordial dwarfism type II to ascertain prevalence and characteristics of cerebrovascular disease and use these data to propose an evidence-based approach to cerebrovascular screening. Of 147 cases identified, 47 had cerebrovascular disease (32%), including occlusive arteriopathy (including moyamoya) and cerebral aneurysmal disease. Occlusive disease occurred in younger individuals, and progression can be both rapid and clinically silent. A reasonable screening approach would be magnetic resonance imaging and angiography of the cervical and intracranial circulation at diagnosis, repeated at yearly intervals until 10 years, and every 2 years thereafter, unless clinical concerns occur earlier. At present it would appear that this needs to be life-long. Families and professionals should be alerted to the potential significance of neurologic symptoms and measures should be taken to maintain good vascular health in affected individuals.



## Introduction

Microcephalic osteodysplastic primordial dwarfism type II (MOPD II) is a rare autosomal recessive condition characterized by severe interuterine growth restriction, severe postnatal growth restriction, microcephaly, osteodysplastic skeletal changes, and generally preserved intellectual function. The phenotype is secondary to mutations in the gene coding for the centrosomal protein pericentrin (PCNT; 21q22). Cerebrovascular disease, both occlusive arteriopathy (including moyamoya) and cerebral aneurysms, were recently reported to be a common feature of MOPD II and to be associated with a high rate of mortality [1,2]. Both these structures of disease are amenable to intervention (revascularization for occlusive disease and surgical clipping/endovascular coiling for aneurysms), and it has been suggested that presymptomatic detection and treatment has the potential to improve outcomes for these children [2]. Having received a number of referrals to our pediatric cerebrovascular service from clinical geneticists, we were prompted to consider formulating an evidence-based approach for cerebrovascular screening in MOPD II. Here we review all reported cases of MOPD II to estimate frequency and characteristics of cerebrovascular disease and propose such evidence-based recommendations about timing and modality of cerebrovascular screening.

## Methods

We undertook a search of Pubmed (1966–September 2012) using the following search terms: “Majewski osteodysplastic primordial dwarfism type II,” “microcephalic osteodysplastic primordial dwarfism type II,” “primordial dwarfism,” “moyamoya,” “aneurysm,” “stroke,” “hemorrhage,” “vasculopathy,” “vascular,” “Microcephalic osteodysplastic

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primordial," "primordial dwarfism," "Seckel," "Pericentrin," "PCNT," "MOPD," "MOPD II." Moyamoya (defined according to Fukui [3]) and other stenosing arteriopathies not strictly meeting these criteria were combined under the category of "occlusive arteriopathy." Cases of "Rupture of CNS vessels" or "intracranial hemorrhage" were categorized as cases of aneurysmal disease. The case reports were reviewed to obtain details of age and modality of presentation of cerebrovascular disease, natural history of cerebrovascular disease and comorbid phenotypic features. Where an article within the literature referenced a case that was published in an earlier article, the most recent genetic and cerebrovascular event data for that patient was included to ensure that the patient was sampled only once in this review. However, because of the lack of identifying data for a number of patients within the literature, it is possible that some cases were multiply ascertained.

## Results

The search yielded 147 cases of MOPD II on the basis of phenotypic features or positive pericentrin gene analysis. Of these, 47 (25 male, 2 undetermined sex) were reported to have cerebrovascular disease (32%) (Table 1). This was occlusive arteriopathy in 14, cerebral aneurysmal disease in six, and a combination of these in seven (the remainder were unspecified). Another three had extracerebral vascular disease (renal artery aneurysm, pulmonary artery stenosis, coronary artery stenosis). Cerebrovascular disease resulted in death in 11 of the 47 patients (23.4%); data on morbidity in the remainder was scant. There were insufficient data to comment on whether specific phenotypic features of MOPD II cosegregated with cerebrovascular disease. Of note, although 13 of the 147 patients with MOPD II had café au lait macules, these were noted in seven of the 47 patients with cerebrovascular disease (14.9%). All of these patients had occlusive arteriopathies, although three also went on to develop aneurysms. Two young patients with occlusive arteriopathy also had cutis marmorata, which was not described in any of the patients with MOPD II without cerebral arteriopathy.

Given the small number of cases reported in the literature, the issue of multiple ascertainment of cases is an important one. In particular, we were concerned about potential overlap between the cases published in the studies of Hall et al. [4] and more recent data reported by Bober et al. [2]. To address this, we reanalyzed the data having removed cases included in Hall et al. [4], because we understand that many of these cases were eventually enrolled in the registry developed by Bober et al. [2]. This reduced the total number of unique MOPD II cases to 91 and the number with cerebrovascular pathology to 40, yielding a prevalence of 44%, similar to that quoted by Bober et al. [2] (52%).

Data on the age of clinical presentation with cerebrovascular disease was very limited. We believed this was an important issue because the predicted age of presentation and structure of cerebrovascular disease would be important determinants of any screening strategy. To maximize the available data, we elected to include data from cases reported by Rauch et al [5,6]. Here the ages of the patients at the time of reporting, rather than the age of clinical presentation of cerebrovascular disease was provided. In total, data on age of presentation were available in 20 of 47 cases. The youngest affected patient was 14 months; in general occlusive disease appeared to present in younger patients compared with aneurysmal disease (Fig 1). This trend was apparent regardless of whether the cases of Rauch et al. [5] were included or not. In logistic regression

**Table 1. Cerebrovascular disease in MOPD II cases**

| Article | Unique MOPD II Cases | PCNT Mutation Known | Vascular Malformation | Aneurysm(s) | Occlusive Arteriopathy | Dual Pathology | Other |
|---|---|---|---|---|---|---|---|
| Rauch et al. [5,6] | 21 | 21 | 8 | 1 | 4 | 1 | 2 |
| Bober et al. [2] | 25 | — | 15 | — | 2 | 2 | 11 |
| Rahme et al. [11] | 1 | — | 1 | — | — | 1* | |
| Codd et al. [12] | 1 | — | 1 | — | — | 1 | |
| Piane et al. [13] | 1 | Yes (1) | 1 | — | 1 | — | |
| Willems et al. [1] | 12 | Yes (12) | 2 | 1 | — | 1 | |
| Waldron et al. [14] | 3 | — | 3 | 1 × multiple | 1 | 1 | |
| Webber et al. [15] | 1 | — | 0 | — | — | — | |
| Galasso et al. [16] | 1 | — | 1 | — | — | — | 1 |
| Griffith et al. [10] | 4 | Yes (4) | 0 | — | — | — | |
| Brancati et al. [17] | 1 | Yes (1)† | 1 | — | 1 | — | |
| Ozawa et al. [18] | 1 | — | 0 | — | — | — | |
| Hall et al. [4] | 56 | Yes (4) | 9 | 1 | — | — | 8 |
| Kantaputra et al. [19] | 2 | Yes (2)‡ | 0 | — | — | — | |
| Kannu et al. [20] | 1 | — | 1 | — | 1 | — | |
| Young et al. [21] | 1 | Yes (1)† | 1 | — | 1 | — | |
| Nishimura et al. [22] | 1 | — | 1 | — | 1 | — | |
| Di Bartolomeo et al. [23] | 1 | — | 1 | 1 × multiple | — | — | |
| D'angelo et al. [24] | 1 | — | 1 | 1 × multiple | — | — | |
| Bober et al. [25] | 9 (34)§ | Yes (26) | — | — | — | — | |
| Műller et al. [26] | 1 | Yes (1) | 1 | — | 1 | — | |
| Kiliç et al. [27] | 1 | Yes (1) | 1 | — | 1 | — | |
| Rigter et al. [28] | 1 | — | — | — | — | — | |
| Total | 147 | 73 | 49 | 6 | 14 | 7 | 22 |

* Nonclassical moyamoya.
† Rauch et al. [5].
‡ Kantaputra et al. [29]. Cases of "rupture of vessels" included as aneurysm.
§ 34 patients in registry, 9 more than quoted in Bober et al. [2].

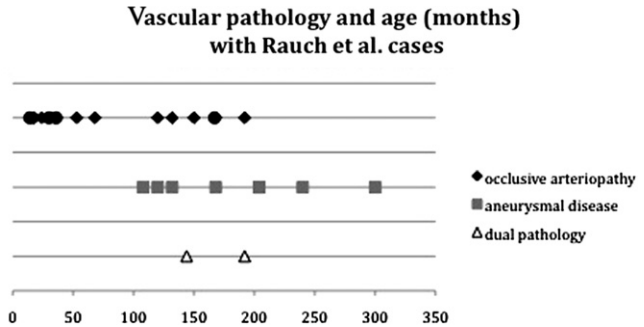


**Figure 1.** Age at initial vascular presentation (months) Vs type of cerebrovascular disease. Circles denote 2 data points of equal value or ±1 month. The figure includes cases from Rauch et al. [5], which may represent age at the time the article was written as data on age of vascular presentation is not explicit within the study.

analysis examining the influence of age on the structure of cerebrovascular disease (occlusive vs. aneurysmal), there was a significant association between younger age and occlusive disease when all the cases were included (odds ratio [OR] 1.03 [95% confidence intervals 1.00 − 1.06]; $P = 0.02$). Removing the Rauch et al. cases (for the reasons discussed above) yielded an OR of 1.02 (95% CI 0.83 − 1.22), $P = 0.07$). We are aware of overinterpreting statistical associations in such a small and incompletely characterized dataset; the data are visually depicted in Fig 1.

Most reports only documented the presence or absence of cerebrovascular disease at a single time point, with little information about imaging modality used. Thus it was difficult to comment on the upper age limit of clinical presentation or indeed on the natural history of cerebrovascular disease once it had been identified. Bober et al. [2] reported a child who had asymptomatic bilateral internal carotid artery narrowing at 14 months, with progression to occlusion by 37 months, resulting in clinically silent cerebral infarcts [2]. Another had early “moyamoya” at 11 years progressing both clinically and radiologically over the next 3 years. An additional patient had normal magnetic resonance imaging and angiography results of the brain at 10 years 11 months but, despite being symptom free, had development of bilateral internal carotid artery occlusion with prominent moyamoya collateral vessels bilaterally at 13 years 11 months, and subsequently a subarachnoid hemorrhage caused by a posterior cerebral artery aneurysm at 17 years. A final patient had normal magnetic resonance brain imaging results at 8 months of age that progressed to cerebral infarction caused by bilateral moyamoya at 18 months. Thus progression of cerebrovascular disease could be both rapid and clinically asymptomatic.

## Discussion

Estimates of frequency of cerebrovascular involvement in MOPD II range from 19% to 52% [2,4]. The phenotypic overlap of MOPD II with other primordial dwarfisms (microcephalic osteodysplastic primordial dwarfism types I/III and Seckel syndrome) and resultant heterogeneity in the literature, as well as the difficulties identifying unique cases, are challenges to determining true frequency. Cerebrovascular disease appears to only be a feature of MOPD II and not of other primordial dwarfisms. Our finding that approximately one third (32%) of patients with MOPD II had cerebrovascular disease is probably an underestimate because it is likely that some individuals had clinically asymptomatic disease at the time being reported. With the strictest criteria for case ascertainment, the published data concur with the prospective observations of Bober et al. [2], that approximately half of people with MOPD II have cerebrovascular disease. Recent interest in this area has been driven by the recognition of a high rate of adverse outcomes associated with cerebrovascular involvement (death in a quarter) and the potential of pre-symptomatic interventions, specifically surgical revascularization for moyamoya [2] or surgical or endovascular treatment of aneurysms, to ameliorate this.

The mechanism by which pericentrin gene mutations cause cerebrovascular disease has yet to be elucidated. Pericentrin is important for cell cycle progression, and it has been suggested that cells deficient in pericentrin are more susceptible to cell death; this may account for the growth restriction in MOPD II [7]. Aside from its role as a centrosomal protein, ubiquitously expressed pericentrin may have organ-specific functions; for example, in mouse models pericentrin has a role in cellular insulin distribution [8]. Given the variable and progressive nature of cerebrovascular disease in MOPD II, it is possible that pericentrin may also have a role in vascular homeostasis. Because not all patients with MOPD II have cerebrovascular involvement, it seems likely that an additional environmental or genetic trigger is required for cerebrovascular pathology to develop, as has been described in other genetic conditions with cerebrovascular involvement [9].

The available data were insufficient to explore whether specific phenotypic characteristics of MOPD II co-segregated with cerebrovascular disease. It is possible that cutaneous lesions indicate a higher risk group, but this remains unproven. Of note, Griffith et al. [10] describe a child with the pericentrin gene mutation with hyperpigmented skin lesions, who had no vascular disease at age 13 years. Reports of vascular involvement in other organs are sparse, and it is unclear whether symptom-free patients should be screened for this.

Data on age of presentation and structure of cerebrovascular disease are important to develop a rational and evidence-based proposal for cerebrovascular screening. From the limited available information, occlusive arteriopathies are clinically manifest at a younger age than aneurysmal disease. We concur with the proposal of Bober et al. [2] that aneurysmal disease likely represents the response of an abnormal vessel to long-term hemodynamic stresses. Hall et al. [4] reported a female patient with MOPD II who had a documented intrauterine vascular accident (reported under “central nervous system”), suggesting that individuals may be susceptible from the earliest stages of life. Although the upper age limit of reported patients with aneurysmal disease was between 18 and 25 years [4,11], this probably reflects reporting bias, and it is likely that the risk of cerebrovascular disease is life-long. The potential for unpredictable rapid asymptomatic progression means that interval of screening for cerebrovascular pathology in these patients may need to be short [2]. Of note, patients can have multiple cerebrovascular disorders at different time points,

and therefore identification of initial disease should not exclude them from future screening.

The limited data do not permit a formal cost-benefit analysis for cerebrovascular screening in MOPD II, but the high rate of cerebrovascular involvement, potential for presymptomatic detection, adverse outcomes untreated, and potential for effective intervention support this strategy. Bober et al. [2] proposed MRI or CT angiography at 12- to 18-month intervals [2]. Through collection of all available data (147 cases) and analysis of the timeline of cerebrovascular disease progression, we have attempted to provide a more robust and evidence-based proposal to that made by Bober et al. [2]. We aim to balance the disadvantages of repeated anesthesia for pediatric imaging or exposure to irradiation with the timely detection of presymptomatic disease. These recommendations (although similar to those made by Bober et al. [2]) are supported by a larger data set and the evidence that younger age is associated with occlusive rather than aneurismal pathology, which may progress rapidly. Given there is no lower age limit for cerebrovascular involvement, we suggest initiating screening at the point of diagnosis with brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the circle of Willis and cervical arteries. Looking at the limited natural history data, and taking into consideration that occlusive disease tends to occur in younger children and has been reported to progress rapidly, we propose that imaging should be repeated at yearly intervals until age 10 years; thereafter, the main focus of screening would be to detect aneurysms, and it seems reasonable to widen the screening interval to 2 years. Naturally clinical concerns should override these recommendations. MRI and magnetic resonance angiography are sensitive for the detection of clinically significant occlusive arteriopathies. Although magnetic resonance angiography may not be the optimal technique for detection of all intracranial aneurysms, it is unlikely that aneurysms below the resolution of magnetic resonance angiography would merit treatment. The advantages of avoiding recurrent exposure to radiation are clear. Where lesions are identified, further characterization, by CT or catheter angiography may be necessary, but we suggest that these techniques are preserved for clinical rather than screening purposes. It is important that imaging is reviewed by clinicians conversant with complex cerebrovascular disease to ensure they are accurately interpreted.

Importantly, clinicians caring for patients with MOPD II, and their families, should be aware that neurologic symptoms (motor/speech problems, headache, seizures, cognitive difficulties) may indicate an evolving neurovascular process. Serial cognitive evaluation should be considered as an indicator of otherwise silent cerebral infarction. General medical care should include measurement and good control of blood pressure and patients should be educated about avoiding other cerebrovascular risk factors. Adopting a consistent strategy and collaborative prospective data collection is important to enable critical appraisal of the validity of the proposed approach.

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