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Neuronal migration disorders in microcephalic osteodysplastic primordial dwarfism type I/III

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Abstract

Microcephalic osteodysplastic primordial dwarfism (MOPD) is a rare microlissencephaly syndrome, with at least two distinct phenotypic and genetic types. MOPD type II is caused by pericentrin mutations, while types I and III appear to represent a distinct entity (MOPD I/III) with variably penetrant phenotypes and unknown genetic basis. The neuropathology of MOPD I/III is little understood, especially in comparison to other forms of lissencephaly. Here, we report postmortem brain findings in an 11-month-old female infant with MOPD I/III. The cerebral cortex was diffusely pachygyric, with a right parietal porencephalic lesion. Histologically, the cortex was abnormally thick and disorganized. Distinct malformations were observed in different cerebral lobes, as characterized using layer-specific neuronal markers. Frontal cortex was severely disorganized and coated with extensive leptomeningeal glioneuronal heterotopia. Temporal cortex had a relatively normal 6-layered pattern, despite cortical thickening. Occipital cortex was variably affected. The corpus callosum was extremely hypoplastic. Brainstem and cerebellar malformations were also present, as well as old necrotic foci. Findings in this case suggest that the cortical malformation in MOPD I/III is distinct from other forms of pachygyria–lissencephaly.

Keywords

Pachygyria; Brain malformation; Lissencephaly; Cobblestone malformation

Introduction

Microcephalic osteodysplastic primordial dwarfism (MOPD) is a rare condition that was initially divided into three phenotypic types [19], categorized under the slender bone dysplasia group of skeletal disorders [31]. Type II is apparently a distinct disorder [13,20,24,33], but types I and III may be variant manifestations of the same entity (also known as Taybi–Linder cephaloskeletal dysplasia) with likely autosomal recessive inheritance [3,10,22,34,37]. Common features in MOPD I and III include severe pre- and post-natal growth retardation, microcephaly, and similar distinctive facies, but dwarfism in type I is more disproportionate with short bowed long bones, less dysplastic pelvis, and no medial spurs of the ischial bones. In contrast, type III is characterized by dolichocephalic skull, elongated clavicles, platyspondyly, marked dysplasia of the pelvis, and enlarged metaphyses [22,29,37]. The prognosis of MOPD types I and III is poor. Death occurs early, generally before 1 year of age [3,10,22,29].

The neuropathologic changes in MOPD I/III are multifocal and variable. Major brain malformations, including hypoplastic frontal lobes, pachygyria, neuronal heterotopia, partial or complete agenesis of the corpus callosum, and agenesis or hypoplasia of the cerebellar vermis, have consistently been described [3,10,13,19,21,25,28,33], but the cortical cytoarchitecture has not been studied in detail.

Here, we present neuropathological findings in a female infant with MOPD, with overlapping features of types I and III. The lissencephalic cytoarchitecture is elucidated using specific molecular markers to identify different cortical layers.

Case history

This female infant was born to a 20-year-old G1P0 Caucasian mother by cesarean section at 33 5/7-weeks gestation. The father was African-American and the parents were non-consanguineous. The family history is non-contributory. The pregnancy was complicated by extreme intrauterine growth retardation and oligohydramnios. The birth weight was 990 g (50% for 28 weeks), length was 33 cm (<26 weeks), and head circumference was 25 cm (<4 SD, 50% for 27 weeks).

Dwarfism and dysmorphic features were identified (Fig. 1), including microcephaly, sloped forehead, small anterior fontanel, unusually textured and sparse hair, periorbital fullness, prominent eyes, broad nasal root, thickened upper lip, shortened and simplified philtrum, micrognathia, extremely small and low-set simple ears, short neck, pigeon-shaped chest, disproportionately short limbs with flexion contractures at the elbows, deficient musculature and edema. The thumbs were hypoplastic, and distal phalanges of the fingers were shortened with clinodactyly of the second digit. The hands had a spade-like appearance with edema and excessive soft tissue. A combination of talipes equinovarus and rocker-bottom feet was present with overriding of the fourth toe by the fifth with markedly thickened plantar creases and edema. The toes were short with hypoplastic or absent nails. At birth, the patient had a patent ductus arteriosus that closed spontaneously. Hearing tests were deferred. Neonatal complications included apnea which resolved, transient unconjugated hyperbilirubinemia, necrotizing enterocolitis treated medically, and retinopathy of prematurity. Postnatal somatic growth was poor, with minimal gain of weight and length. She suffered from severe

gastroesophageal reflux and difficult oral feeding. Nissen fundoplication and repair of bilateral inguinal hernias were attempted at age 2 months, but failed due to intubation difficulties attributed to laryngotracheal stenosis. Diagnosis of MOPD was made at this time based on significant pre- and post-natal growth retardation, distinctive craniofacial features, alopecia, skeletal manifestations, and limb contractures. At 10 months of age, she was diagnosed with seizures. She died at 11 months. Three days before death, she developed fever (39.4°C), papular chest rash, vomiting, and bloody diarrhea, complicated 3 days later by acute fulminant hepatic failure progressing to multiorgan failure/systemic inflammatory response syndrome. Respiratory syncytial virus was detected by laboratory testing. A complete autopsy was performed.

Genetic testing

Amniocentesis showed a normal female G-banded karyotype, 46, XX at 450–500 bands resolution. Array comparative genomic hybridization using a bacterial artificial chromosome platform (SignatureChipWG™™; Signature Genomics, Spokane, WA) did not identify any genomic loss or gain for 1,543 loci represented on the microarray. Chromosomal breakage studies utilizing mitomycin C and diepoxybutane also yielded normal results.

Radiological studies

Skeletal survey at 3 months of age (Fig. 2a–e) showed delayed epiphyseal ossification, a hypoplastic mandible, overtubulation of the long bones with thick cortices and narrow medullary spaces, diffuse sclerosis of the vertebrae and skull base, and minimal platyspondyly. Fingers appeared bent with well-formed phalanges, while phalanges of the toes were deficient. Pelvis views showed bilateral hip dislocation. A bowed humeral diaphysis was also seen.

At age 9 months, magnetic resonance imaging (MRI) revealed bifrontal lissencephaly, with temporal, parietal, and occipital lobes affected to lesser degrees (Fig. 2f–g). An interhemispheric defect or cyst was noted, and appeared to communicate with the third ventricle. A parenchymal defect was found in the right parietal lobe, consistent with porencephaly. The thinned adjacent cortex and meninges demonstrated a linear hypointense gradient echo signal, corresponding to mineralization as noted on computerized tomography (CT) obtained in the first 3 weeks of life (not shown). The anterior commissure was present, while the corpus callosum appeared extremely small or absent. The deep grey nuclei, thalamus, midbrain, pons and cerebellum showed no specific malformation. Magnetic resonance angiography demonstrated patent cerebral arteries.

Neuropathological examination

The brain was removed (236 g; normal, 1 year female 940 g) and fixed in 4% buffered formalin for 4 weeks. The fixed brain without cerebellum and brainstem weighed 162 g; the fixed brainstem and cerebellum weighed 82 g (infratentorial/total brain ratio 33.6%; normal 14.3%). Selected brain regions were sampled, embedded in paraffin, routinely stained with hematoxylin and eosin (H&E), and submitted for immunohistochemistry as described below.

Methods

Immunohistochemistry was performed on 4-μm-thick paraffin sections from selected brain regions. The following mouse monoclonal antibodies were used: anti-glial fibrillary acidic protein (GFAP) (1:1,000) from Chemicon; N52 anti-neurofilament 200KD (phosphorylated and non-phosphorylated) (1:150) from Millipore; anti-microtubule-associated protein

MAP-1B (1:200) from Chemicon; and anti-calbindin D-28K (1:3,000) from Sigma. The following rabbit polyclonal antibody was used: anti-calretinin (1:1,000) from Swant. Biotinylated secondary anti-mouse (1:200) and anti-rabbit (1:400) antibodies were purchased from Vector Laboratories. Staining was done by the avidin–biotin complex (ABC) method using the Vectastain kit (Vector Laboratories). Incubation with diaminobenzidine (DAB) from Sigma was done according to the manufacturer's instructions, followed by counterstaining with Mayer's hematoxylin.

Cortical thickness was measured in the frontal and temporal lobes, using macroscopic photographs that included rulers.

Results

General autopsy findings

A 4-mm atrial septal defect was present (patent foramen ovale). The left ventricle was small, with a markedly thickened wall and asymmetric hypertrophy of the subaortic portion of the interventricular septum. The lungs were firm with a purple congested appearance. The right lung demonstrated patchy consolidation of airways due to neutrophil-rich infiltrates; neither viral cytopathy nor significant bronchiolitis was seen. The lymph nodes lacked well-formed germinal centers, but displayed patchy hemorrhage and apoptosis. Both kidneys demonstrated scattered mineralized tubular casts and many eosinophilic granular casts. The femoral growth plates showed mildly disorganized columnar arrangement of chondrocytes, particularly in the proliferative zone. The zone of provisional ossification seemed long, with sparse osteoid, and the metaphysis was mildly hypotrabecular. The resting cartilage extended laterally beyond the periosteum of the metaphysis, and at these lateral edges the apposition of bone with resting cartilage was abnormal. No intervening growth plate was observed.

Macroscopic brain pathology

The cerebrum showed a smaller right than left hemisphere (Fig. 3). Pachygyria was noted, worst in the hypoplastic frontal lobes, which furthermore displayed midline attachment due to fusion of leptomeninges plus glioneuronal heterotopia. The inferior hemispheric surfaces were simplified and the rhinal sulcus was absent. In the lateral temporal lobe, only inferior and superior temporal gyri were distinguished. Porencephaly was present in the right parietal lobe. The corpus callosum was severely hypoplastic, with midline attachment only at the genu. The medial left hemisphere showed calcarine and parietooccipital sulci, but the right hemisphere showed absence of the parieto-occipital sulcus, presumably due to gyral malformation associated with porencephaly. The cortical grey matter was thickened, measuring 7–8 mm (normal, 3.4 mm [2]), and the grey/white ratio was increased. The hippocampus was small. A partially cystic, yellow necrotic lesion measuring 5 mm in its greatest dimension was visible in the left frontal lobe, and additional small necrotic foci were seen in the left and right frontal white matter, caudate nucleus, thalamus, internal capsule, and right midbrain tegmentum. The cerebral peduncles were small and almost absent on the right. The vermis was small. The pyramids appeared hypoplastic, while the inferior olives appeared relatively spared.

Brain histopathology

Histological examination showed thickening of the cortex in all lobes, regions of neuronal disorganization with poorly formed layers, and blurred boundaries between cortical grey and white matter. The histological appearance of lissencephalic cortex varied among lobes. Superficial layers of the frontal cortex appeared hyperconvoluted, with invaginations of layer I resembling polymicrogyria (Fig. 4). The frontal cortex appeared roughly 3-layered,

with a sparsely cellular molecular layer I containing small-to-medium sized neurons. Below this was a relatively thick layer of mostly medium-to-large sized pyramidal cells, designated layer II. The large pyramidal cells in this layer were randomly distributed and oriented. MAP-1B, a marker of layer V (and to lesser extent, layer III) in normal cortex [12], demonstrated the somata of some large neurons, along with segments of dendrites and axons in this layer. Fewer pyramidal neurons showed expression of N52 antigen (likewise a layer V marker in normal cortex). Calretinin (a marker of layer II/III in normal cortex) identified small bipolar interneurons. Layer III was thickest, extending more than half the width of the mantle, and contained mostly small-to-medium sized neurons with no clear organization. Axon bands oriented vertically to the cortex showed N52 immunoreactivity. No hypocellular or myelinated layer was detected within cortex. Leptomeninges overlying the frontal cortex exhibited a thick crust of glioneuronal heterotopia. Numerous GFAP immunoreactive glia, and several N52, MAP-1B, and calretinin-immunopositive neurons and neuropil were seen in the heterotopia (Fig. 4).

The temporal cortex exhibited a more typical “6-layered” appearance, albeit abnormally thick (Fig. 5). Pyramidal cells labeled by MAP-1B and N52 were located mainly in layer V. The cells were sometimes organized in small clusters. In addition, a smattering of MAP-1B and N52 immunopositive pyramidal cells were found in other layers, especially layer III. Calretinin-immunopositive interneurons were prominent in layers II and III, although some bipolar cells showed calretinin expression even in deeper cortical layers.

The occipital cortex mainly demonstrated a 3-layered pattern of lissencephaly (Fig. 6), with many MAP-1B and N52 immunopositive medium-sized pyramidal cells in layer II. Calretinin immunoreactive cells were located mainly in layer II, although a few were seen in layers I and III as well. In addition, a few occipital gyri exhibited 6-layered lamination (again, excessively thick), similar to the temporal cortex in this case.

Subpial gliosis (confirmed by GFAP immunoreactivity) was evident in all lobes, along with widespread gliosis of the white matter, and hippocampal gliosis. The hippocampus and the dentate gyrus were markedly hypocellular (Fig. 7c). MAP-1B immunoreactive neurons were localized in the pyramidal and molecular layers, while N52 immunopositive medium-sized cells and axon bands were localized in the molecular layer. The basal ganglia and the thalamus showed no obvious histological abnormality.

In the cerebellum, focal loss of Purkinje cells was seen (Fig. 7a). Interestingly, a few Purkinje and granular neurons were heterotopic in the leptomeninges (Fig. 7b). The vermis was hypoplastic. Cells of the deep cerebellar nuclei appeared normally organized, and some showed N52 immunopositivity.

The medulla oblongata demonstrated absence of the arcuate nucleus. The inferior olives had slightly simplified convolutions, with numerous MAP-1B and some calretinin-immunopositive neurons (Fig. 7d). The nucleus cuneatus showed few N52, MAP-1B, and calretinin immunoreactive neurons, while cells of the nucleus gracilis had strong N52 immunopositivity. The nucleus ambiguus was marked by the presence of MAP-1B immunopositive cells. Neurons were moderately decreased in the basis pontis, where only weak immunoreactivity for calretinin and MAP-1B was found. Similar immunoreactivity was observed in the superior olivary nuclei.

Necrotic lesions in the hemispheric white matter, deep grey nuclei and midbrain demonstrated cystic degeneration with foamy macrophages, siderophages, and surrounding GFAP immunoreactive astrocytes, consistent with remote infarcts. The cortex lining the porencephalic defect showed severe GFAP immunopositive gliosis including calcium deposits and ferruginated neurons.

Discussion

Neuropathological data from previously reported patients with MOPD have been scant [3,10,15,22,24,29,32]. The present case of an 11-month-old girl with MOPD I/III provides new details regarding the neuropathology of this devastating condition. Comparison to other patients is difficult, since most other reported patients with MOPD I/III died shortly after birth. Nevertheless, features shared between the present case and previously reported cases included microcephaly, frontal lobe hypoplasia, abnormal gyral patterning (lissencephaly/pachygyria), partial agenesis of the corpus callosum, and leptomeningeal heterotopia (Table 1). Novel findings in the present case included hypoplasia of the hippocampus and dentate gyrus, brainstem anomalies (absent arcuate nucleus, simplified inferior olivary nuclei, and decreased basis pontis neuronal populations), and severely abnormal cortical lamination.

In this case, distinct abnormalities of cortical lamination (summarized in Fig. 8) were characterized in different lobes using layer-specific neuronal markers. The normal cerebral cortex contains a great diversity of pyramidal and non-pyramidal neuron types that have been studied most extensively in layer V [1,11,16,21,23,38]. Pyramidal neurons are generated in the cortical ventricular zone (VZ) and subventricular zone (SVZ) [6,11,30,39]. The γ -aminobutyric acid (GABA)ergic interneurons in cortex and hippocampus are generated mainly in the ganglionic eminences of the ventral forebrain and reach the cortex by tangential (non-radial) cell migration [27,39], although in humans, some cortical interneurons also originate from progenitors in the cortical neuroepithelium [16]. Many diverse families of molecules including calcium-binding proteins, axon guidance molecules, cytoskeletal proteins, transcription factors, and secreted morphogens exhibit layer-specific expression patterns, but only few of these can be assessed in formalin-fixed paraffin sections [6,12,21,23,38].

Our analysis revealed interesting differences between the cortex in MOPD I/III and other types of lissencephaly. Type I lissencephaly has classically been described as having a 4-layered neocortex [8]. However, recent genetic studies have shown that type I lissencephaly is remarkably heterogeneous, with linkage to multiple genes including *LIS1*, *DCX*, *TUBA1A*, *VLDLR*, *ARX*, and *RELN* [25,30]. Accordingly, distinct histopathologic subtypes of lissencephaly type I have been described [7], varying from 2- to 6-layered and differing not only among brains, but also among different lobes of the same brain. The various histopathologic subtypes were correlated with underlying genetic defects, although some cases with 2-layered lissencephalic cytoarchitecture had no confirmed genetic changes [7]. *LIS1* mutations exhibited the classic 4-layered cytoarchitecture, while *DCX* and *ARX* defects each showed unique lissencephalic architecture [7]. Mutations of *TUBA1A* were associated with defects in neuronal migration, differentiation and axonal transport, causing distinct abnormalities in the laminar architecture of the cortex and hippocampus [14,17]. In contrast, type II (cobblestone) lissencephaly is severely disorganized due to widespread breakdown of the glia limitans and basal lamina, and shows little evidence of lamination.

In the current case, the frontal cortex exhibited a 3-layered cytoarchitecture, with large pyramidal neurons distributed in layer II. Interneurons were seen in layer II around the pyramidal neurons, as well as in deeper cellular layers. The frontal cortex also showed extensive leptomeningeal glioneuronal heterotopia indicating a component of glia limitans breakdown, albeit less severe than in type II lissencephaly. The temporal cortex, despite abnormal thickness, disclosed organization similar to normal 6-layered cortex. The occipital cortex showed both 3-layered lissencephalic organization, and roughly ordered 6-layer lamination in different gyri. Overall, the cortex in MOPD I/III exhibited some histopathologic features of both type I and type II lissencephaly, along with distinct

macroscopic features of severely decreased brain size, marked frontal hypoplasia and widespread pachygyria.

MOPD I/III has not yet been linked to any defined genetic abnormality. Some evidence indicates that an MOPD I/III locus lies on chromosome 2q [18], but to date, the molecular basis of this disorder has been obscure [3,20]. In contrast, MOPD II has been definitively linked to mutations in the pericentrin (*PCNT*) gene [26,28,36]. Seckel syndrome, a form of microcephaly with some phenotypic similarities to MOPD II, has also been associated with *PCNT* mutations, although such cases may actually be more compatible with a diagnosis of MOPD II [36]. Usually, Seckel syndrome is associated with mutations in the *ATR* gene [9].

Regarding infratentorial structures, lissencephaly type I has been associated with defects of the brainstem and cerebellar structures that are typically mild, consisting of corticospinal tract degeneration, olivary dysplasia and Purkinje cell heterotopias, and mild dysplasia of cerebellar granule cells [4,7]. Similarly, the medulla oblongata in the current case demonstrated absence of the arcuate nucleus, simplified convolutions of the inferior olivary nuclei, and slightly decreased basis pontis neuronal populations. In addition, the vermis appeared relatively hypoplastic, and focal Purkinje cell loss was noted.

Overlying the cortex was a layer of heterotopic glioneuronal tissue, predominantly on the rostral convexities. Heterotopia is a common finding in MOPD as described in previous reports [3,10,15,22,29,32,37]. Hypoplasia of the hippocampus and the dentate gyrus has not been reported previously in MOPD I/III. However, changes in the hippocampal formation have been associated with neuronal migration abnormalities and/or agenesis of the corpus callosum [5], and therefore, are consistent with other findings in this case.

In addition to the primary CNS malformations, multiple old infarcts were found in the hemispheric white matter, deep grey nuclei, and brain stem of this patient. Similar disruptions have been described in MOPD type I/III by Winter et al. [37]. The focal infarcts and porencephaly presumably resulted from hypoxic-ischemic injury, occurring both pre- and post-natally, in the context of a complex clinical condition. Porencephaly typically results from severe hypoxia-ischemia around midgestation. During postnatal life, the patient experienced respiratory difficulties and received mechanical ventilation support. On the other hand, MRA revealed normal vascular anatomy. In MOPD II, cerebrovascular abnormalities have been consistently observed, including Moyamoya disorder and multiple intracranial aneurysms [13,35]. It is possible that cerebrovascular abnormalities are also a component of MOPD I/III, occurring at lower penetrance than in MOPD II.

The neuropathological findings in this patient implicate perturbations to multiple cellular mechanisms during early brain development. The malformations may be largely attributed to decreased neurogenesis in progenitor zones, impaired postmitotic cell migration along radial and non-radial axes, defective basal lamina or glia limitans development, and possibly excessive neuronal death. However, the exact mechanisms of pathogenesis will remain uncertain until a genetic basis can be defined, and animal models produced.

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Fig. 1.

The patient at age 9 months. Note **a** sloping forehead, sparse hair and eyebrows, periorbital fullness, and small low-set ear. **b, c** Talipes equinovarus and rocker-bottom foot with overriding of the fourth toe by the fifth, and markedly thickened plantar creases and edema. **d** Spade-like hand along with brachydactyly and clinodactyly of the index finger. (Written informed consent was obtained from the patient's mother for showing the images in this figure.)

Fig. 2.

Radiological findings. Flat-plate images at age 3 months showed: **a** Patchy sclerosis of the bones and bilateral hip dislocation. **b, c** Mildly slender long bones and narrow intramedullary cavities. **d** Fingers were bent, albeit with well-formed phalanges. **e** Deficient phalanges of the toes. MRI of the brain at age 9 months (**f** axial T1-weighted, **g** coronal T2-weighted) revealed diffuse bifrontal hypoplasia and lissencephaly, with temporal, parietal and occipital lobes affected to a lesser extent. The corpus callosum was not identified; the deep grey nuclei and thalamus were unremarkable. Prior hemorrhages or infarcts were noted in white matter. The large interhemispheric defect (**g**) seemed to communicate with the third ventricle

Fig. 3. Brain at postmortem examination. **a** The cerebrum was asymmetric with smaller right hemisphere than the left; gyri were reduced and thick, worse frontal, with midline attachment of the frontal lobes due to leptomenigeal fusion (*black arrows*). **b** Lateral view demonstrated inferior and superior temporal gyri; porencephaly was seen in the right parietal region with a thin membrane (*white arrow*). **c** Inferior view demonstrated the simplified hemispheric surface with absent rhinal sulci; a yellowish necrotic area was found in the right midbrain tegmentum (*dashed back arrow*). **d** Sagittal sections showed a hypoplastic corpus callosum (*black arrows*), crossing only at the genu. **e** Coronal slices of the right hemisphere. The cortex was thick, measuring 0.7–0.8 cm (*dashed black lines*), while white matter was very thin. The hippocampus was small. The porencephalic defect was transmural (*white arrow*). Cystic yellow necrotic foci were seen at the grey–white interface and in deep grey nuclei (*black arrows*). Scale bars in **a–e** indicate centimeters

Fig. 4. Histopathology of frontal cortex showing 3-layered lissencephaly. The layers *I*, *II*, *III*, and white matter (*WM*) are indicated on the H&E stained section. The leptomeninges demonstrated a crust of glioneuronal heterotopia (*white asterisk*). The superficial layer (*I*) of frontal cortex appeared hyperconvoluted, resembling polymicrogyria. Layer II consisted of disorganized medium- to large-sized pyramidal cells, many labeled with MAP-1B and N52 immunoreactivity. Interneurons labeled by calretinin were distributed mainly in layer II. Layer III contained small-sized neurons, many labeled with MAP-1B, as well as N52 immunoreactive axon bundles orientated radially in the cortex. The boundary between grey and white matter was blurred. (*Insets* show higher magnifications of *boxed areas*.)

Fig. 5. Histopathology of temporal cortex. H&E staining showed the 6-layered pachygyric cortex designated by Roman numerals *I* to *VI*, and the white matter (*WM*). Note leptomeningeal glioneuronal heterotopia (*white asterisk*). Layer *V* contained large pyramidal neurons labeled with MAP-1B and N52. Layer *VI* contained N52-immunopositive, radially oriented axon bundles (*lower inset*). Calretinin immunolabeled interneurons were seen mainly in layer *II*. The boundary between grey and white matter was not well defined. (*Insets* show higher magnifications of *boxed areas*.)

Fig. 6. Histopathology of occipital cortex. H&E demonstrated neuronal disorganization with primitive 3-layered lissencephaly, and a poorly defined boundary with white matter (WM). MAP-1B and N52 immunopositive pyramidal cells were found in layer II. Interneurons labeled by calretinin were mainly distributed in layer II. (*Insets show higher magnifications of boxed areas.*)

Fig. 7.
a Cerebellum, demonstrating focal loss of calbindin-immunoreactive Purkinje cells. **b** Heterotopic granule neurons and Purkinje cells were found in the cerebellar leptomeninges. (*Inset* shows higher magnification of *boxed area*.) **c** The hippocampus and dentate gyrus were hypocellular (H&E). **d** MAP-1B immunostaining demonstrated the inferior olives with moderately simplified convolutions. The pyramidal tract was severely hypoplastic and virtually absent

Fig. 8.

Schematic illustrations of the 3-layered lissencephaly of the frontal and the occipital lobes, and 6-layered pachygyric cortex of the temporal lobe, compared to normal cortex as labeled by MAP-1B, N52, and calretinin. The normal cortex has a relatively hypocellular molecular layer I (*brown, yellow*). Layer II contains calretinin immunolabeled neurons (*red*), found also in layer III along with small pyramidal neurons (*blue*). Layer IV contains small granular neurons (*yellow*), while layer V, the internal pyramidal cell layer, highlights medium-to-large MAP-1B and N52 positive pyramidal cells (*grey*). Layer VI is the fusiform and multiform layer (*green, purple, brown*), and below this is the white matter (*striped white–grey*). In the present case, layer I of the frontal and the occipital lobes was moderately cellular and contained various neuron types including MAP-1B, N52, and calretinin-immunopositive cells. Below this was a disorganized pyramidal cell layer highlighted by MAP-1B and N52 immunopositive cells designated layer II. Layer III was thickened and consisted of mostly small MAP-1B and N52 positive pyramidal cells, calretinin labeled cells, and other small- to medium-sized unlabeled cells. The temporal lobe had a relatively normal cytoarchitecture, although markedly thickened. The white matter was reduced in all lobes

Table 1

Brain malformations reported in MOPD type I/III

	Number of cases	Brain autopsy	Microcephaly	Hypoplastic frontal lobes	Gyral abnormalities	Subcortical or leptomeningeal heterotopia	Cerebellar heterotopia	Callosal agenesis or hypoplasia	Vermian agenesis or hypoplasia
Berger et al. [3]	1	1	1/1	1/1	1/1	1 lm/1	0/1	1 ch/1	0/1
Haan et al. [10]	1	1	1/1	0/1	1/1	1 lm/1	0/1	1 ca/1	1 vh/1
Kozłowski et al. [15]	1	1	1/1	0/1	1/1	1 sc/1	0/1	1 ca/1	0/1
Meinecke and Passarge [22]	2	1	2/2	1/1	1/1	0/1	0/1	1 ca/1	0/1
Sigaudy et al. [29]	4	1	4/4	1/1	1/1	0/1	0/1	1 ch/1	1 va/1
Taybi and Linder [32]	2	1	2/2	0/2	2/2	2 sc/2	0/1	2 ca/2	0/2
Winter et al. [37]	1	1	1/1	1/1	1/1	1 lm/1	1/1	1 ch/1	0/1
Present case	1	1	1/1	1/1	1/1	1 lm/1	0/1	1 ch/1	1 vh/1
Total	13	8	13/13 (100%)	6/9 (66.7%) ^a	9/9 (100%) ^a	7/9 (77.8%) ^a	1/9 (1.11%) ^a	9/9 (100%) ^a	3/9 (33.3%) ^a

sc subcortical, lm leptomeningeal, ca callosal agenesis, ch callosal hypoplasia, va vermian agenesis, vh vermian hypoplasia

^a Some malformations were not evaluated in all cases, so the numbers of cases evaluated for each malformation are indicated as the denominator where appropriate