OCULOCEREBROCUTANEOUS SYNDROME: THE BRAIN MALFORMATION DEFINES A CORE PHENOTYPE

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ABSTRACT

Introduction: Oculocerebrocutaneous syndrome (OCCS) is characterized by the presence of orbital cysts and an/microphthalmia, focal a/hypoplastic skin defects, skin appendages and brain malformations. Whereas eye and skin abnormalities are well described, the neuropathological features generally have not been well delineated. To date, 28 patients with an unequivocal diagnosis of OCCS have been reported with a preponderance of males.

Methods: We evaluated the brain imaging studies, clinical records, photographs and/or pathological material of 2 new and 9 previously reported patients.

Results: We found a remarkably consistent pattern of malformations in eight of 11 patients, consisting of frontal predominant polymicrogyria and periventricular nodular heterotopia, enlarged lateral ventricles or hydrocephalus, agenesis of the corpus callosum sometimes associated with interhemispheric cysts, and a novel mid-hindbrain malformation. The latter consists of a giant and dysplastic tectum, absent cerebellar vermis, small cerebellar hemispheres in most cases, and a large posterior fossa fluid collection. We hypothesize that the mid-hindbrain malformation is pathognomonic for OCCS.

Discussion: The eye and skin features of OCCS show considerable overlap with several other syndromes, such as encephalocraniocutaneous lipomatosis, oculo-auriculovertebral spectrum, and focal dermal hypoplasia, none of which has a comparable pattern of brain malformations. In particular the unique mid-hindbrain malformation distinguishes OCCS also from related syndromes with comparable forebrain anomalies. The described pattern of malformation thus helps in differentiating OCCS from other entities. The mid-hindbrain malformation points to a defect of the mid-hindbrain organizer as the underlying pathogenetic mechanism.

INTRODUCTION

Oculocerebrocutaneous syndrome (OCCS), also known as Delleman syndrome, is a rare multiple congenital anomaly-mental retardation syndrome characterized by the triad of eye, brain and skin malformations, sometimes associated with other features such as craniofacial clefts, skull or rib defects, and urogenital anomalies. We have found reports of 28 patients with unequivocal OCCS, with a preponderance of affected males.[1][2] This number of reported patients excludes patients with a possible diagnosis of OCCS or who have features of overlapping syndromes, in particular encephalocraniocutaneous lipomatosis (ECCL) and oculoauriculo-vertebral spectrum (OAVS). The cause of OCCS is still unknown.

The eye malformations consist mainly of cystic an/microphthalmia and colobomata, while the skin abnormalities consist of skin appendages and focal aplasia or hypoplasia. Both have been well described.[1] Many reports mention cerebral cysts, but this might refer to several different anomalies such as arachnoid, porencephalic or posterior fossa cysts, ventricular enlargement, or any other abnormal fluid collection. Several patients have had agenesis of the corpus callosum. However, many of the reports predate modern brain imaging modalities and even recent reports rarely give a detailed description. A systematic description of the brain malformation in OCCS is not available.

We therefore reviewed the brain abnormalities in a series of 11 patients with OCCS, using a variety of brain imaging studies and one autopsy report. While some of the images were old and incomplete, we were still able to document a remarkably consistent pattern of malformations that includes a novel mid-hindbrain malformation.
METHODS
We obtained all available data regarding the brain in 11 patients with OCCS, including medical records with reports of brain imaging studies, clinical photographs (Fig. 1), and all or portions of the original brain imaging studies (Fig. 2-3 and Supplementary Figures). The brain imaging studies included brain MRI in 7 patients, cranial CT in 4 patients, and pneumoencephalogram (PEG) in one patient; one patient had both MRI and CT. We also reviewed an autopsy report and limited pathological tissue from the child who had the PEG.

RESULTS
Clinical reports and review of brain abnormalities

Patient 1
This boy was born with a large cystic left eye, right microphthalmia, eyelid colobomas and other ocular anomalies, and typical skin appendages.[3] When re-evaluated at 6 years, he had severe mental retardation, intractable epilepsy, severe right hemiparesis, and decreased tactile sensation.

Brain MRI (Fig. 2 and 3A-D) showed severe polymicrogyria (PMG) with very thick cortex in the left frontal, temporal and perisylvian regions, at least one underlying periventricular nodular heterotopia (PNH), enlarged lateral ventricles greater on the left, and agenesis of the corpus callosum (ACC). The midbrain was angled forward, resulting in a nearly horizontal aqueduct that abruptly enlarged into the 4th ventricle about half way down the midbrain. The midbrain tectum was massively enlarged (~3 cm in length), rotated far upwards of the normal position behind the midbrain tegmentum, and indented inferiorly by the enlarging aqueduct into an arched shape. The superior cerebellar peduncles were long, thick and straight, extending almost vertically downward to join the cerebellar hemispheres, which were almost normal in size. The cerebellar vermis was completely absent, although a small and unusual white matter tract connected the two hemispheres. The 4th ventricle was continuous with a large posterior fossa fluid collection, suggesting cystic enlargement. Similar images from a normal MRI study are shown for comparison in Supplementary Figure S1.

Patient 2
This boy was born to Mexican parents who were second cousins. His birthweight was 3.66 kg, length 51 cm, and head circumference 36 cm. He had bilateral orbital cysts, a cleft left nostril with denuded skin, left macrostomia, multiple skin lesions, and right cryptorchidism. The skin lesions included a fleshy mass with tags and pits on the left cheek; tags in the middle of his forehead on top of a hemangioma, on his scalp to the left of the anterior fontanelle, and at the tip of the coccyx; a focal aplastic defect above the right and a crescent shaped one above the left ear (Fig. 1A-B), another focal aplastic skin lesion just below the xiphoid process, and three deflated blister-like lesions on the right neck (Fig. 1A). The left orbital cyst enlarged and was removed. Pathological examination demonstrated malformed retinal and glial tissue with dystrophic calcifications. The mass on the cheek was also removed together with a maxillary exostosis beneath it. Pathological examination confirmed a hamartoma. At one year, he had seizures and developmental delay.

Brain MRI at 8 months (Fig. 3E-H) demonstrated asymmetric PMG that involved the frontal and perisylvian region, several PNH along the anterior body of the left lateral ventricle, mildly enlarged ventricles and ACC. The PMG, PNH and ventricular enlargement were all more severe
on the left. The upper midbrain was angled forward, resulting in a nearly horizontal aqueduct. The aqueduct was short, and abruptly enlarged into an extra ventricle just above the 4\textsuperscript{th} ventricle. The tectum was again massively enlarged (~4 cm in length), rotated upward and curved, providing the roof of the extra ventricle. The cerebellar vermis was absent and the hemispheres were probably small from the limited images available. The 4\textsuperscript{th} ventricle communicated with a large posterior fossa fluid collection.

Patient 3
This girl was born to a 33-year-old Hispanic woman and her 32-year-old unrelated husband. Her birth weight was 3.77 kg, length 50 cm, and head circumference 35 cm. She had multiple anomalies including left microphthalmia, a disorganized mass of tissue with a skin appendage and cleft in the left lower lid near the outer canthus (Fig. 1C), and multiple skin lesions consisting of tags in the left nares, the periumbilical region, the right groin and posterior to the anus; punched out aplastic defects in the left scalp and right heel, and multiple circumscribed hypoplastic defects with depression of subcutaneous tissue and lack of hair over the left leg. On pathological exam, the swelling near the left eye was a benign hamartoma with 46,XX chromosome constitution, while the hypoplastic skin defects were neuroectodermal developmental dysplasias. An omphalomesenteric duct remnant was found in the umbilical cord. Her heart was structurally normal but displaced in the chest by an anterior diaphragmatic evagination that was repaired. A few new skin lesions were seen during the first year, but not thereafter. Serial neurological exams demonstrated dysarthria, hypotonia and a mild right hemiparesis. Cognitive functioning at 3 years was normal. An electroencephalogram was normal. Otoacoustic emmission and sound field testing documented normal hearing bilaterally.

Brain MRI at 1 day (Fig. 3I-L) showed asymmetric PMG in the left frontal and perisylvian regions, possible PMG in the right frontal lobe, and mildly enlarged left lateral ventricle. No heterotopia were seen but the resolution was low. The corpus callosum was dysmorphic with a thin body and absent splenium. The midbrain was angled slightly forward and the lower aqueduct was mildly enlarged. The midbrain tectum was enlarged (~1.5-2 cm) but not rotated upward. The cerebellar vermis was absent and both hemispheres small, especially the left. The 4\textsuperscript{th} ventricle was large and communicated with a large posterior fossa fluid collection.

Patient 4
This boy was blind because of bilateral cystic anophthalmia, and had typical skin appendages. He has been published in detail previously.[1] [4] At 8 years, he had severe mental retardation and epilepsy.

Brain MRI (Fig. 3M-P) showed frontal PMG extending to the perisylvian, parietal and temporal regions, PNH along both frontal horns and lateral bodies of the lateral ventricles, mildly enlarged lateral ventricles, and complete ACC. The cortical malformation was more severe on the right. The midbrain was anteverted resulting in a nearly horizontal orientation of the aqueduct, which was mildly enlarged in its inferior portion. The tectum was moderately enlarged (1.5-2 cm) and round. The cerebellar vermis was absent and the hemispheres both very small. The 4\textsuperscript{th} ventricle was continuous with a large posterior fossa fluid collection.
Patient 5
This boy had left cystic microphthalmia and eyelid coloboma, and typical skin lesions of OCCS.[1][4] At 26 months, he had moderate mental retardation and epilepsy.

Brain MRI (Fig. S2C-D) at 7 months and later CT scans (Fig. S2E-H) showed frontal PMG extending an uncertain distance posteriorly, more severe on the right. The lateral ventricles were enlarged left greater than right and separated by several interhemispheric cysts posterior to the 3rd ventricle, some with increased signal indicating lack of communication with the ventricles, that suggest total ACC. Lower images showed an enlarged tectum with prominent and probably horizontal aqueduct, absent cerebellar vermis, moderate hypoplasia of the right and severe hypoplasia of the left cerebellar hemispheres, and a large posterior fossa fluid collection.

Patient 6
This boy was one of the original patients from the first report by Delleman et al., and was reported again at age 17 years.[5][6][7] He presented with right cystic microphthalmia, bilateral eyelid coloboma, bilateral focal hypoplastic skin defects including a typical crescent-shaped defect behind the ear, and skin appendages. He also had severe mental retardation.

Cranial CT scans (Fig. S2I-L) performed at ages 4 and 7 years showed a thick and irregular cortex typical of PMG diffusely that was most severe in the smaller right frontal lobe. The lateral ventricles were asymmetrically enlarged with the right much larger than left, and separated by a midline cyst that appeared to be an extension of the third ventricle. The latter suggests partial ACC. The midbrain was dysplastic with an enlarged aqueduct on one image and an unusual round mass of tissue on the highest image. The pons appeared mildly small, the vermis absent, and the cerebellar hemispheres small especially on the right. A large fluid collection was located just behind the cerebellum that probably communicated with a low occipital skull defect, consistent with a meningocele.

Patient 7
This boy was patient 2 in the original paper reporting OCCS.[5][6] He had bilateral cystic microphthalmia and eyelid colobomas, typical skin lesions, severe mental retardation and a seizure disorder. He died at 2 years from complications of hydrocephalus.

Only a low resolution CT scan (Fig. S2M-P) from 1977 was available for review, and the gyral pattern was too indistinct to assess. The lateral ventricles were mildly enlarged, greater on the right, and widely separated suggesting complete ACC. The tectum was large and dysplastic, the vermis absent, and the cerebellar hemispheres were hypoplastic, with the right side being more severely affected. The midbrain appeared to connect to the cerebellar hemispheres directly. Serial scans were reported to show progressive hydrocephalus.

Patient 8
This German boy presented in the neonatal period with bilateral cystic anophthalmia, skin appendages in the periorbital region and on his trunk and the scalp, and numerous focal skin defects. He died at age 1 year.[7]

A pneumoencephalogram (PEG) (Fig. S2A-B) done years ago showed asymmetric, enlarged and widely separated lateral ventricles typical of ACC, probable hydrocephalus, a large posterior fossa fluid collection, and a skull defect in the occipital midline suggesting a meningocele. An autopsy demonstrated PMG, hydrocephalus, an interhemispheric cyst and a malformation of the
midbrain tectum, which was 5 cm in length and extended beyond the cerebellum. We were able to obtain a single block of tissue from the cortex, most likely from the occipital lobe, that confirmed a severe cortical dysplasia, although preservation was too poor to classify the type. Several intraabdominal neurofibromas were found along the sympathetic chain.

Patient 9
This 3-year-old Belgian boy had eyelid and iris colobomas but no other eye anomalies, and atypical skin abnormalities consisting of small periorbital nodules, a small skin appendage on the thumb and linear skin defects on the trunk and arms.[8]

A suboptimal and incomplete MRI (Fig. S3A-B) showed a normal or possibly mildly dysplastic gyral pattern, enlarged and asymmetric lateral ventricles, larger on the left, and partial ACC with a small frontal remnant near the genu. Several loculated cysts with high signal (protein content) were seen within the lateral ventricles. The brainstem and cerebellum appeared grossly normal.

Patient 10
This Dutch boy had unilateral cystic microphthalmia, characteristic skin lesions and mild mental retardation. He was also reported previously.[9]

The report of his MRI noted enlarged ventricles, but none of these images were available for review. A single midsagittal MRI (Fig. S3C) showed a normal gyral pattern along the medial surface and total ACC. The pons appeared moderately narrow or flat, but the midbrain including the aqueduct and tectum, and cerebellar vermis appeared normal.

Patient 11
This Russian baby was born with a huge anophthalmic orbital cyst on the left, which had already been diagnosed prenatally by ultrasound. He had typical skin lesions located on the left side or the midline. In addition, he had bilateral cryptorchidism and mild anomalies of the ribs. Apart from mild hypotonia, his psychomotor development was reported to be normal at two years. He has been published in abstract.[10] In addition, clinical data and photographs were available.

Cranial CT scan was reported as normal except for the eye. A single suboptimal image was available for review (Fig. S3D). It showed a mildly enlarged space anterior to the left temporal pole, normal brainstem and cerebellum, and left cystic anophthalmia.

DISCUSSION
OCCS is a rare malformation syndrome that heretofore has been diagnosed based on its eye and skin abnormalities. We reviewed the brain abnormalities of 11 patients with OCCS which are summarized in Table 1. Due to the rarity of OCCS, we included patients ascertained over many years and as a result, many of the available brain imaging studies were suboptimal and incomplete. We were able to perform detailed reviews in 5 (patients 1-5), adequate review in one (patient 6), and limited reviews in five (patients 7-11) of these patients. Despite this, we were able to document a remarkably consistent malformation in eight of the 11 patients and unexpectedly found a novel mid-hindbrain malformation. The three remaining patients had similar but less severe forebrain abnormalities, but lacked the mid-hindbrain malformation, which we suspect to be pathognomonic for OCCS.
**Typical OCCS brain malformation**
In the eight patients with the most typical malformation complex, the forebrain malformation consisted of (1) frontal predominant PMG, (2) PNH that were always located beneath the PMG, (3) complete or partial ACC sometimes associated with interhemispheric cysts, and (4) enlarged 3rd and lateral ventricles complicated by hydrocephalus in four patients.

The novel mid-hindbrain malformation was found in all eight patients, and consisted of a giant tectum, absent vermis and large posterior fossa fluid collection. The midbrain tegmentum was flexed forward making the aqueduct nearly horizontal in four of the five patients with complete MRI studies. The giant and dysplastic tectum was rotated upward well above the normal position, and appeared to form an arch over the enlarged lower aqueduct in several patients. The cerebellar hemispheres were missing or hypoplastic with a dysplastic foliar pattern in seven of eight patients. The 4th ventricle communicated widely with a large posterior fossa fluid collection, sometimes associated with an occipital meningocele. All of these anomalies excluding the midline malformations were asymmetric in all 8 patients. The more severe PMG, more numerous PNH, larger lateral ventricle and smaller cerebellar hemisphere were always on the same side when we could assess this.

The key forebrain malformations of PMG, PNH, enlarged ventricles and ACC are relatively common individually, but occur together in only a few syndromes, as we will review. Thus, this pattern should be very helpful for diagnosis. The mid-hindbrain malformation has previously been confused with typical DWM, which should not be surprising. The usual diagnostic criteria for DWM include hypoplasia of the cerebellar vermis, and widely open 4th ventricle outflow tract that communicates with a large posterior fossa fluid collection, or so-called cystic enlargement of the 4th ventricle.[11][12] While the typical OCCS mid-hindbrain malformation described here includes each of these criteria and so could be labelled as DWM, we think this would lead to ongoing diagnostic confusion. The OCCS mid-hindbrain malformation includes many other anomalies, and is clearly much more severe and complex than DWM. Despite considerable experience in evaluating brain malformations in many different disorders, we have not seen this mid-hindbrain malformation in any other context. We hypothesize that all or most patients with the giant tectum-absent vermis malformation have OCCS, and that most but not all patients with OCCS have the mid-hindbrain malformation.

**Incomplete OCCS brain malformation(s)**
Only suboptimal imaging studies were available for the remaining three OCCS patients, but at least two had ACC and none had the mid-hindbrain malformation. The gyral pattern and cortex were either normal or mildly dysplastic in patient 9; resolution of the MRI was too low to be sure. This could not be assessed in the other two patients. Patient 9 also had mildly enlarged lateral ventricles with several cysts within them that appeared quite different from the midline cysts seen in two patients from the more typical OCCS group. Two of the three (patients 10 and 11) had typical eye and skin changes of OCCS, although patient 10 was less severely affected than any other patient. In contrast, patient 9 had atypical linear skin defects with unusual localization. However, one patient with less typical eye and skin lesions was also found in the group with the typical brain phenotype. We do not yet have enough evidence to determine whether OCCS in these three patients results from the same cause as OCCS in more typical patients.
The differential diagnosis of OCCS

Our results have implications for the differential diagnosis of several related syndromes. Some have overlapping eye and skin changes such as ECCL, OAVS, and focal dermal hypoplasia (FDH or Goltz syndrome). Others have similar brain malformations, especially Aicardi syndrome and a recently recognized group of syndromes with PNH and PMG.

ECCL and OAVS have considerable overlap with OCCS with regard to the skin, eye and other associated abnormalities. Extensive lipomatosis of the brain and spinal cord are characteristic of ECCL.[13] In addition, asymmetries of the cerebral hemispheres, an abnormal gyral pattern, cortical calcifications, porencephalic or arachnoid cysts and dilated lateral ventricles have been described repeatedly.[14][15][16][17] However, mid-hindbrain malformation has never been described in ECCL. In OAVS, only a minority of the patients have developmental delay. A few have hydrocephalus or various brain malformations, but no pattern has emerged except that patients with microphthalmia, clefts or other evidence of a severe phenotype are more likely to have developmental problems.[18] Several patients with (possible) OCCS and overlap with OAVS have been reported.[19][20][21][22] One boy had PMG over the frontal lobes, ACC and a midline cyst and so likely had OCCS.[20] Several other patients with overlapping features of OAVS and OCCS have had massive hydrocephalus without the brain anomalies characteristic of OCCS. In this group, the combination of severe hydrocephalus with anophthalmia or severe microphthalmia and clefts favors OAVS.

FDH is a X-linked disorder affecting predominantly females characterized by a combination of cutaneous, ocular, neurological and skeletal features.[23] Focal hypoplastic skin lesions often with herniation of fatty tissue, and linear pigmentation are the predominant cutaneous features. In contrast to OCCS, the skin lesions commonly follow the lines of Blaschko indicating a mosaic defect. Skin tags are papillomas, in contrast to the (mostly periorbital) hamartomatous tags in OCCS. Ocular features are very diverse and mostly affect the anterior chamber; chorioretinal and iris colobomas are reported but orbital cysts have not been described. Skeletal defects of the hands and feet may occur. X-rays show striation of the bones in most patients. Whereas many patients are mentally retarded, brain malformations have rarely been described and do not correspond to the brain malformations seen in OCCS.

Aicardi syndrome. The typical OCCS brain malformation overlaps substantially with the brain malformation seen in Aicardi syndrome, which is thought to be X-linked with embryonic lethality in males. Although the typical eye anomalies (chorioretinal lacunae) are different and the skin generally is normal, other features of Aicardi syndrome overlap considerably with OCCS. For example, the brain malformation in Aicardi syndrome includes PMG, rare PNH, enlarged ventricles (but not typically hydrocephalus) and ACC.[24][25] Interestingly, a few patients with Aicardi syndrome had DWM.[26] Other overlapping features include microphthalmia, coloboma of the optic nerve, scalp lipoma, cleft lip/palate and costovertebral defects.

PNH-PMG syndromes. We have recently delineated several syndromes with PMG, PNH and other anomalies (W.B. Dobyns, unpublished data). The frontal-perisylvian subtype consists of PNH lining the lateral body and frontal horns of the lateral ventricles, overlying PMG that is most severe in the perisylvian area, and sometimes ACC and mild cerebellar vermis hypoplasia. The malformation is usually symmetric, and no other anomalies have been observed. A posterior subtype consists of PNH of the temporal horns, trigones and occipital horns of the lateral ventricles, overlying PMG most severe in the temporal, parietal and occipital lobes, and frequent
ACC and hypoplasia of the entire cerebellum. This malformation complex is usually asymmetric, but again no other anomalies have been found, in particular not the mid-hindbrain malformation described in this paper.

Pathogenesis of OCCS
Analysis of available data regarding the pathogenesis of OCCS provides two important clues, both of which support a genetic etiology for OCCS despite the lack of familial recurrence. First, a striking preponderance of males has been reported, including 10 of the 11 patients reported here. The only female in our series had the typical brain malformation, which suggests that she has the same syndrome. Among the six other female patients reported, one did not undergo brain imaging,[6] one had a normal cranial CT scan,[27] and four had malformations that may fit the classical brain phenotype.[28][29][30][31] These data suggest that OCCS may be X-linked.

Second, the unusual mid-hindbrain malformation suggests an abnormality of the isthmus organizer, which is located between the embryonic midbrain and the first segment of the hindbrain (rhombomere 1 or Rh1) and controls development of the midbrain, upper pons and cerebellum. Recent experimental data in the mouse show that two transcription factors (the rostrally-expressed Otx2 gene and caudally-expressed Gbx2 gene) repress each others’ expression, forming a sharp boundary between the midbrain and Rh1. This establishes the position of the developmental signaling center for this region, and ultimately defines the posterior limit of the midbrain and the anterior limit of the cerebellum.[32][33][34] One possible interpretation of the giant tectum-absent vermis malformation in OCCS is that the boundary between the midbrain and hindbrain has been shifted caudally in the dorsal portion of the embryonic neural tube, which is less extensive than observed in Gbx2 knockout mice and so appears provisionally unique.

In conclusion, the reported pattern of brain malformations in patients with OCCS extends the phenotype, and should prove very useful in establishing the diagnosis and differentiating it from other entities, in particular from syndromes with overlapping skin and eye features. These observations should contribute to unravelling the underlying pathogenetic mechanism. The novel mid-hindbrain malformation points to a defect in early pattern formation at the stage when the isthmus organizing center is established, setting up the boundary of the midbrain and cerebellum.

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REFERENCES
Table 1. Brain abnormalities in patients with OCCS

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Legend: ACC: agenesis of the corpus callosum; F: frontal; HEM hypo: cerebellar hemisphere hypoplasia; IHEM: interhemispheric; LV: lateral ventricles; MCD: malformations of cortical development; MIDB: midbrain; R/L asym: right-left asymmetry; L>R: left side more severe; R>L: right side more severe; PF: posterior fossa; PMG: polymicrogyria; PNH: periventricular nodular heterotopia; PS: perisylvian; P: parietal; T: temporal; +: present; -: absent; …: data not available. *Partial ACC, †Suboptimal or incomplete study; ‡Hydrocephalus; §Cephalocele (meningocele); ¶Autopsy report; **Supplementary material
FIGURE LEGENDS

**Figure 1.** Clinical features of patients 2 and 3. Note focal aplastic defects above the ears and blister-like lesions in patient 2 (A-B). Patient 3 (C) shows left microphthalmia, and a cleft and mass of tissue with a skin appendage in the left lower lid near the outer canthus.

**Figure 2. The classical OCCS brain malformation.** Brain MRI from patient 1 demonstrates details of the OCCS brain malformation. Images through the cerebral hemispheres show an irregular surface, reduced sulcation, thick 10-15 mm cortex and reduced white matter typical of polymicrogyria involving the left frontal, temporal and parietal lobes (F-H, J-P and white arrows in G, K and L). The lateral ventricles are mildly enlarged, especially on the left, and the corpus callosum is absent (E, I and J, black arrows in I and J).

Images through the posterior fossa show a massively enlarged tectum and absent cerebellar vermis. The midbrain tegmentum is flexed forward but otherwise normal. The aqueduct is short and nearly horizontal (horizontal white arrow in E), and enlarges into the 4th ventricle behind the upper midbrain. The 4th ventricle is continuous with a large posterior fossa fluid collection. The midbrain tectum is greatly enlarged (black arrows in E, H and O) and rotated upward, and appears to form an arch over the enlarged aqueduct (black arrows in G, L and N). The cerebellar vermis is completely absent (B-G and L-P, black arrows in B, F, K and P). The cerebellar hemispheres are nearly normal in size, and seen in the midline due to the missing vermis (white arrow in E). The superior cerebellar peduncles are thick and dysplastic, descending vertically from the dysplastic midbrain to the cerebellar hemispheres (horizontal black arrow in K). The lower brainstem and spinal cord appear normal.

**Figure 3. The classical OCCS brain malformation.** MRI from patients 1-4 also demonstrate the typical OCCS brain malformation. Views of the cortex show polymicrogyria (horizontal white arrows in B-D, G-H, K-L and N-P), which is asymmetric in all four patients with more severe changes on the left (the right side of the images) in patients 1-3 (A-L) and on the right in patient 4 (M-P). Several periventricular nodular heterotopia are seen adjacent to the frontal horns and anterior bodies of the lateral ventricles (black arrows inside the ventricles in B, H and P). The white matter is poorly myelinated in patients 2-4 (E-P) (patient 1 is older). The corpus callosum is absent in patients 1, 2 and 4 (A, E and M), and dysplastic in patient 3 (black arrow in I).

Images through the posterior fossa show a massively enlarged and upwardly rotated tectum (long white arrows in A, E, I and M) and absent vermis (vertical arrows in J and N) in all four patients. In all, the midbrain is angled more forward than normal leading to a short, horizontal aqueduct, enlarging prematurely into the 4th ventricle (A, I, M) or appearing to form an abnormal extra ventricle behind the midbrain (E); the 4th ventricle is continuous with a large posterior fossa fluid collection. The cerebellar hemispheres are small and have a dysplastic foliar pattern in patients 3 and 4 (J and N), and are seen in the midline due to the absent vermis (short white arrows in A, E, I and M).
Oculocerebrocutaneous syndrome: the brain malformation defines a core phenotype

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In the Original article titled, Oculocerebrocutaneous syndrome: the brain malformation defines a core phenotype (J Med Genet 2005;42:913-921) the supplementary figures were missing from the paper. The supplementary figures are available on the JMG website at http://www.jmedgenet.com/supplemental.