Neuroradiology (1994) 36: 473–476

Paediatric Neuroradiology

Neuro radiology

MRI of the brain in muscle-eye-brain (MEB) disease

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Received: 18 November 1992/Accepted: 7 September 1993

Abstract. Muscle-eye-brain (MEB) disease belongs to the spectrum of rare congenital syndromes with migration disorders of the brain and muscular dystrophy, along with the Walker-Warburg syndrome and Fukuyama congenital muscular dystrophy. Their features overlap, and differential diagnosis presents some difficulties. We examined the brain of 10 patients with MEB using high-field MRI and found a uniform pattern consisting of a pachygyria-type cortical migration disorder, septal and corpus callosum defects and severe hypoplasia of the pons in 7 of them.

Key words: Muscle-eye-brain disease – MRI

Muscle-eye-brain disease (MEB), first described by Santavuori et al. in 1977 [1], is an inherited condition characterised by congenital muscular dystrophy, a neuronal migration disorder of the brain, and ocular changes including progressive myopia, retinal dystrophy and optic atrophy. Children with MEB usually present with muscular hypotonia, visual problems and severe developmental delay. Some die of respiratory failure during the first or second decade, others survive to adulthood, in spite of the severe clinical disturbances.

Disordered cerebral migration is also associated with congenital muscular dystrophy in Fukuyama congenital muscular dystrophy (FCMD) [2–4]. Radiologically, FCMD is characterised by pachygyria and extensive white matter lesions. Although myopia and other ocular abnormalities have occasionally been described, they are not a constant feature of FCMD.

The Walker-Warburg syndrome (WWS) [5–11] includes lissencephaly type II cortical migration disorder and retinal dysplasia, microphthalmia and anomalies of the anterior segment of the eye. The discovery of congenital muscular dystrophy in WWS raised nosological questions about these clinically overlapping disorders.

Although about 300 cases of FCMD are known in Japan, MEB and WWS are rare; most reports consist of a few cases. MEB was originally described in 9 Finnish patients 15 years ago; the series now consists of 23 patients.

A neuropathological examination of two MEB patients revealed an agyria-pachygyria type neuronal migration disorder with cerebellar and brain stem abnormalities (12). A CT scan study of 12 patients showed enlarged lateral ventricles and white matter changes (13), but failed to visualize the cortical anomaly.

Magnetic resonance imaging (MRI) is superior to CT in delineating migration disorders [14–16]. We describe MRI findings in 10 patients with MEB.

Patients and methods

We saw 21 children with MEB at the Children's Hospital of the University of Helsinki, and 2 at the Children's Hospital of the University of Kuopio, between 1970 and 1993. The diagnostic criteria included mental retardation, severe myopia, and myopathic changes on muscle biopsy. The presentation in 21 cases was as floppy infants with suspected blindness. All had severe, progressive myopia (> 6 dioptres), retinal degeneration and optic atrophy. Two siblings (patients 9, 10) were included in the group at the age of 40 and 46 years, after MEB was diagnosed in a relative. Their clinical deficits were significantly milder than those of the others, in all respects. Six patients died before MRI was available; we examined 10 of the 17 surviving patients, 5 males and 5 females, including three sets of siblings (1 and 2, 5 and 6, 9 and 10). The age of the patients varied from 4 to 60 years at the time of the MRI study.

MRI examination was performed with a 1.0 Tesla unit. Most patients needed mild sedation because of restlessness and involuntary movements. A double echo sequence (SE 2200/22–90) was used to obtain proton density and T2-weighted images in axial and coronal planes, the slice thickness being 5 mm. T1-weighted images (SE 500 or 600/15) were obtained with axial and sagittal orientation and 4 mm slice thickness.

The images were interpreted by two radiologists. The gyral pattern and cortical thickness were studied in each lobe in axial and coronal images. The state of myelination and possible white matter abnormalities were assessed on the axial T2-weighted images and sagittal images were used to study the midline structures.

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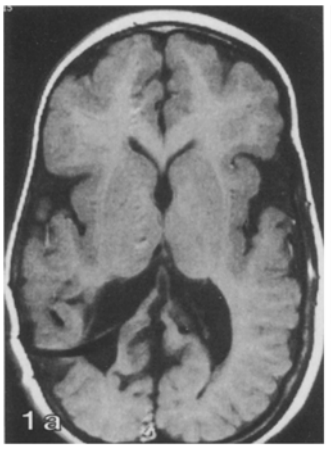

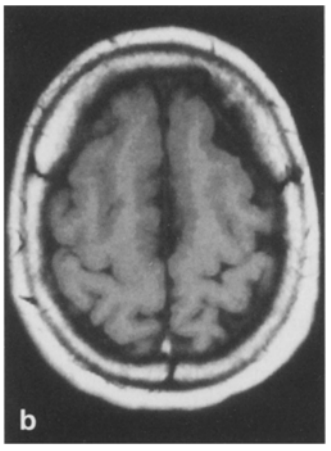

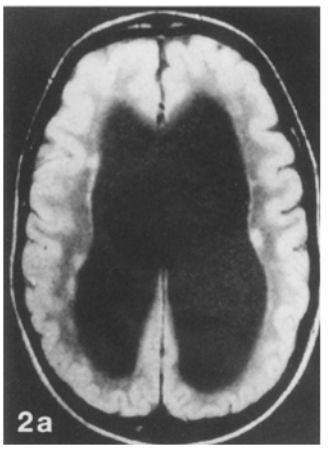

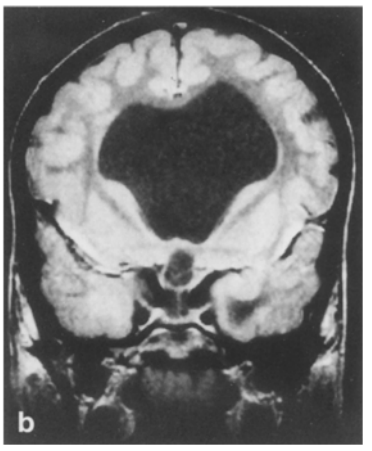

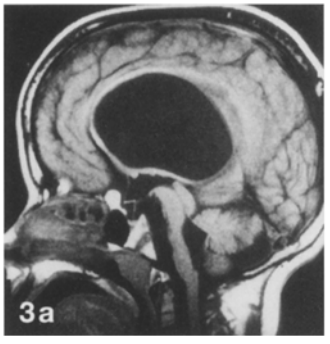

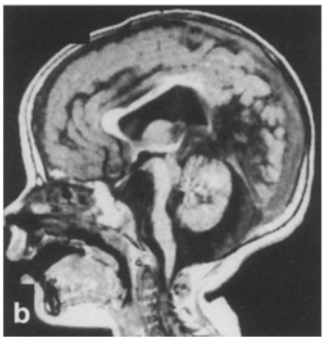

Fig. 1 a, b. Patient 3. T1-weighted axial MRI. **a** Pachygyria in the frontal and temporal lobes. The gyri are few and broad based with slightly thickened cortex. The frontal opercula are small and the insular cortex is exposed. Note the missing interventricular septum. The ventricles have been shunted for hydrocephalus. **b** Verrucous dysplasia: the pachygyric frontal cortex has an uneven, nodular surface

Fig. 2 a, b. Patient 4. Proton density-weighted MRI. **a** Axial: Subependymal nodular heterotopia. Small, focal lesions in the ventricular wall are similar in intensity to the grey matter. The interventricular septum is missing. **b** Coronal: large ventricles and absent septum

Fig. 3 a, b. Hypoplasia of the pons. Sagittal T1-weighted images. **a** Patient 5. Complete absence of the pontine bulge and hypoplasia of the inferior vermis. The genu and rostrum of the corpus callosum are present, but the splenium is thin and dysplastic. **b** Patient 1. The splenium is absent. The pons is hypoplastic

Results

A similar developmental anomaly, consisting of a pachygyric disorder of cortical migration, total or partial absence of the septum pellucidum, dysplasia of corpus callosum and hypoplasia of the posterior fossa structures, was seen in seven patients, including two pairs of siblings (Table 1). Pachygyria was seen most often in the frontal temporal and parietal lobes. The gyri were few and broad based with an uneven, nodular surface. Agyric areas were not encountered (Fig. 1). The grey-white matter boundary was not smooth but showed some interdigitations. The thickness of the cortex was normal or slightly increased. The frontal opercula were incompletely developed and the Sylvian fissures were wide, exposing the insular cortex. One patient also had small heterotopic subependymal nodules (Fig. 2 a).

The lateral and third ventricles were enlarged in 5 patients, the trigones and occipital horns usually more so than the frontal horns. A ventriculoperitoneal shunt had been placed in three infants because of increasing head circumference and gradually enlarging lateral ventricles. None of the patients showed signs of increased intracranial pressure at the time of the MRI.

The rostral parts of the corpus callosum were always present although they were thin in patients with ventricular enlargement. The splenium was dysplastic and thin in four patients and absent in two (Fig. 3). The interventricular septum was totally absent in 6 patients and partially so in one (Figs. 1, 2, 4 b). No other signs of incomplete separation of the hemispheres were encountered. Neither schizencephaly nor a cephalocele was seen in any patient.

There were white matter abnormalities in six patients, usually small areas of high signal in periventricular white matter; three patients had also small subcortical high signal foci. Only one patient had large confluent lesions, in the periventricular and deep white matter.

Midsagittal T1-weighted images revealed an almost total absence of the pontine bulge in seven patients (Fig. 3). The inferior vermis and cerebellar tonsils were hypoplastic and the posterior cranial fossa was small. In four patients there were multiple small lesions, giving high signal on T2-weighted and low signal on T1-weighted images, on the cranial and lateral cortices of the cerebellar hemispheres (Fig. 4).

The appearances in cases 8, 9 and 10 were different. Patient 8, a very severely affected 17-year-old boy, had clinical features consistent with MEB in infancy, but the progression of his ophthalmological findings was atypical.

He showed supratentorial and cerebellar cortical atrophy without signs of migration disorder. He had a normally shaped pons. The deep and subcortical white matter gave high signal on T2-weighted and low signal on T1-weighted images, resembling the unmyelinated white matter of infancy. Patients 9 and 10, with very mild clinical features, had only cerebellar and brain stem atrophy without signs of migration disorder or midline anomalies.

Table 1. MRI findings in MEB

Patient, sex/age (years)	Migration disorder	Ventricular enlargement	Midline anomalies	White matter lesions	Cerebellum	Brain stem
1. f/4	frontal, temporal	no (shunt)	S, Sp absent	PV ++ SC ++	inferior vermis absent	hypoplastic pons
2. f/8	frontal, temporal	no (shunt)	S, Sp absent	PV ++ SC ++	inferior vermis absent; small cysts	hypoplastic pons
3. f/8	frontal, temporal	no (shunt)	S absent; Sp dysplastic	PV ++ SC ++	inferior vermis absent	hypoplastic pons
4. f/13	frontal, temporal, parietal	+++	S absent; Sp dysplastic	PV ++	inferior vermis absent; small cysts	hypoplastic pons
5. m/15	frontal, temporal, parietal, occipital	+++	S absent; Sp hypoplastic	N	inferior vermis absent	hypoplastic pons
6. m/19	frontal, temporal, parietal	++	S absent; Sp hypoplastic	N	inferior vermis absent	hypoplastic pons
7. m/33	frontal, temporal, parietal	+	S incomplete	PV +++	inferior vermis absent; small cysts	hypoplastic pons
8. m/17	N	++	Sp thin	arrested myelination	atrophy	atrophy
9. m/55	N	N	N	N	atrophy	atrophy
10. f/60	N	N	N	N	atrophy	atrophy

N, normal; PV, SC, periventricular, subcortical high signal; S, septum pellucidum; Sp, splenium of corpus callosum; +, ++, +++, slight, moderate, marked

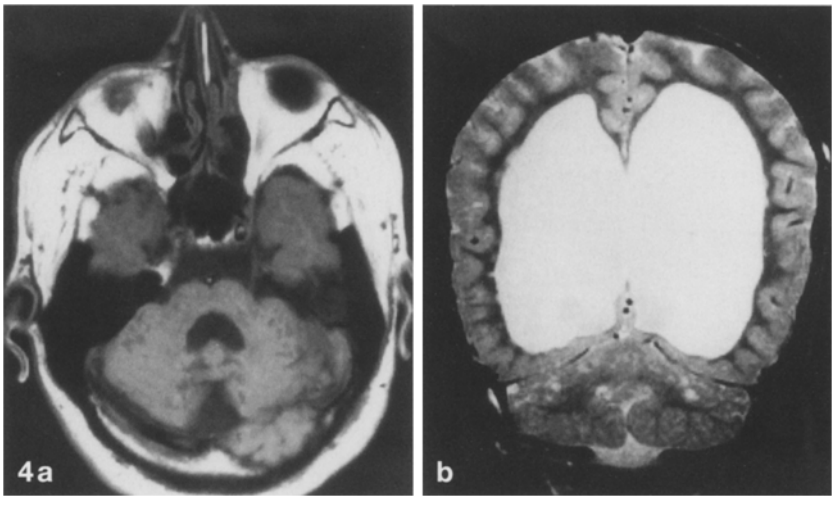

Fig. 4 a, b. Migration disorder of the cerebellar cortex.
a Patient 7. Axial T1-weighted image. Small low-signal lesions are seen on the lateral cortex of the cerebellar hemispheres. The ventral pons is flat.
b Patient 4. T2-weighted image. The lesions are hyperintense

Discussion

We found a uniform malformation consisting of cortical migration disorder, defects of the septum pellucidum and corpus callosum and hypoplasia of the pons in seven of our ten patients. Haltia et al. [12] reported sharply demarcated occipital agyric areas and a universal pachygyric pattern without horizontal lamination of the cortical layers in two patients with MEB, which they classified as type II lissencephaly. A pachygyria-type disorder with few, coarse gyri and shallow sulci was also seen in our patients. The cortical thickness was normal or only moderately increased and the grey-white matter interface showed interdigitations instead of a smooth, linear outline. Agyric areas were not seen in our images. The discrepancy can be explained by variations in the severity of the migration disorder. The uneven, nodular surface of the gyri was also noted by Haltia et al. and is consistent with the verrucous dysplasia described by Barth [17]. It has also been reported in the WWS [8]. The cortical migration disorder of MEB seems thus to be neuropathologically similar to but of milder degree than that seen in the WWS.

Midline fusions, agenesis of the corpus callosum and cystic enlargement of the posterior fossa, typical of WWS [6, 8–10], were not seen in our patients. Absence of the septum pellucidum is reported in association with holoprosencephaly, schizencephaly, the Chiari II malformation and aqueduct stenosis [18], none of which were seen in our patients.

Ocular involvement in MEB is typically a malformed globe, leading to severe myopia, not hypoplasia of the optic nerve, as in septo-optic dysplasia.

White matter changes are typical of FCMD [19, 20]. They become less marked with age and are regarded as

an extreme form of delayed myelination. White matter abnormalities were reported in MEB by Santavuori et al. [13], who found low density areas on CT in 7 of 12 patients. Our patients showed high signal areas in the white matter on T2-weighted images, but the changes were variable in appearance and distribution, generally very subtle and unrelated to the age of the patient. Only patient 7 showed large, confluent white matter changes similar to those described in FCMD, but the lesions could hardly be attributed to delayed myelination in a 33-year-old individual. White matter changes thus do not seem to represent a typical finding.

Hypoplasia of the ventral pons with abnormally situated pyramidal tracts is common in lissencephaly [17]. The pons was extremely flat in all seven of our typical cases. A hypoplastic posterior cranial fossa, reported in the WWS [8], was seen in 6 of our patients. Cerebellar migration disorders are commonly associated with lissencephaly [6, 11, 17]. Takada et al. [21] described a cerebellar cortical migration defect with multiple small cyst-like cavities in FCMD. Punctate lesions in the cerebellar hemispheres of three of our patients are likely to represent this type of migration disorder. These radiological features have not, to our knowledge, been reported previously.

The two siblings with no signs of migration disorder were included in the study after MEB was diagnosed in a relative; their clinical presentation was exceptionally mild. The third patient with atypical MRI findings had a very severe clinical presentation and unusual progression of the ophthalmological findings. The MRI findings raise a question about the diagnostic criteria. At present it is uncertain whether these three patients represent clinical heterogeneity in MEB or another disease.

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