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Congenital muscular dystrophy, brain and eye abnormalities: one or more clinical entities?

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Abstract. Four children with congenital muscular dystrophy (CMD), eye and brain abnormalities are described. Their clinical and neuroradiological features are compatible with a diagnosis of Walker-Warburg syndrome (WWS), according to the criteria proposed by Dobyns et al. (i.e., presence of type II lissencephaly, typical cerebellar and retinal malformations, CMD), who also conclude that WWS is indistinguishable from the muscle-eye-brain disease (MEBD) described by Santavuori. On the basis of our own experience and two recently published series, we emphasize certain features that are different in patients with WWS and patients with MEBD, which make their inclusion in the same syndrome dubious.

Key words: Lissencephaly – Congenital muscular dystrophy – Hydrocephalus – Walker-Warburg syndrome – Muscle-eye-brain disease – Fukuyama congenital muscular dystrophy

Introduction

The association of congenital muscular dystrophy (CMD) with brain and eye malformations has been reported in several clinical syndromes: Fukuyama congenital muscular dystrophy (FCMD) [10], muscle-eye-brain disease (MEBD) [20], cerebro-oculo-muscular syndrome (COMS) [3], cerebro-ocular dysplasia-muscular dystrophy (COD-MD) [24] and Walker-Warburg syndrome (WWS) [5]. It is still under debate whether these clinical entities are separate diseases or different expressions of the same syndrome [5, 8, 12, 13, 14, 22, 24, 28]. In 1989, Dobyns et al. [6] stated that WWS is identical to COMS, COD-MD, and MEBD, proposing the diagnostic criteria for WWS.

The present paper describes four Italian children with very severe psychomotor retardation, congenital muscular dystrophy, and cerebral and ocular malformations, discussing their compatibility with a diagnosis of WWS according to Dobyns' criteria. On the basis of our own experience and a review of two recently reported series [16, 21], it seems that certain different features are emphasized in patients with WWS and MEBD, which make their grouping in a same syndrome dubious.

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Case reports

Case 1

M. R. was the second child of related parents. Her brother had died at 1 month (case 2), diagnosed as having WWS. The girl was born at term after an uneventful pregnancy and was admitted to hospital for low birth weight (2200 g), pendular nystagmus, and hydrocephalus.

At 17 months of age, when first evaluated in our department, she was dystrophic with severe motor and mental retardation and marked hypotonia; deep tendon reflexes were absent and bilateral Babinski sign and joint contractures at the lower extremities were present. Serum creatine kinase (CK) concentration was 3900 U/l (normal value <150 U/l) the serum lactate dehydrogenase (LDH) concentration <450 U/l and pathological changes on muscle biopsy were consistent with the diagnosis of CMD.

Ophthalmological examination revealed bilateral irregular retinal pigmentation, right retinal coloboma, and persistence of the hyaloid artery. Cerebral computed tomography (CT) showed severe tetraventricular dilatation, a thin and smooth cortical mantle, posterior fossa cyst, absence of the septum pellucidum and corpus callosum, and diffuse white matter hypodensity. Generalized clonic seizures with ocular deviation (both to right and left) had developed since 5 months of age and infantile spasms since the age of 9 months.

EEG showed high-amplitude θ activity with intermixed short runs of very fast rhythms (14–16 Hz). Multifocal abnormalities (slow spikes and spikes and waves) were also recorded. Adrenocorticotropic hormone (ACTH) and several anti-epileptic drugs failed to achieve seizure control.

Chromosomal analysis was normal. Dystrophin was found to be present in the muscle biopsy in normal amounts and normal size by the immunoblotting technique. The girl died at 3 years old without showing any mental or motor development. The parents denied consent for autopsy.

Case 2

M. I. was the older brother of the patient in case 1. Massive hydrocephalus, bilateral microphthalmia, severe hypotonia, and poor feeding were reported. He died at the age of 1 month.

Postmortem examination was denied by the parents. The clinical diagnosis was WWS.

Case 3

This boy, F. R., was the first child of healthy, unrelated parents with an unremarkable family history. Congenital hydrocephalus was diagnosed during the pregnancy by echography. A ventricular-amniotic shunt was performed at 30 weeks' gestation and cesarean section at 34 weeks.

Replacement of the ventricular peritoneal shunt was done soon after delivery. The patient's weight at birth was 2230 g. Generalized hypotonia, impaired sucking, and very poor psychomotor development were reported by the parents when the child was first examined in our department at 8 months of age. At that time, generalized hypotonia with no postural control and weak deep tendon reflexes were evident; profound mental retardation and irregular eye movements were also observed.

The serum CK concentration was 3052 U/l; electromyography (EMG) showed a myopathic pattern. Muscle histology was consistent with CMD, with dystrophin present in normal amounts and normal size (immunoblot).

Ophthalmological findings included pale optic disk and bilateral retinal dysplasia. Visual evoked potentials, obtained by flash stimulation, showed normal P_1 and P_2 latencies with a particularly prominent P_1 wave. The electroretinogram response was bilaterally unrecordable.

CT scan demonstrated a smooth cortical surface with enlarged sylvian fissures and lateral ventricles, absence of the septum pellucidum, periventricular white matter hypodensity, cerebellar vermis hypoplasia.

From 8 months of age, the child presented partial seizures with secondary generalization and infantile spasms by 13 months of age.

The EEG was characterized by θ activity with an amplitude which became progressively very high. From the age of 18 months, abnormally rapid rhythms (9–13 Hz) mixed with θ activity were recorded, especially over the temporal regions.

The boy is now 5 years old and is still profoundly hypotonic and mentally retarded. Despite treatment with ACTH and several anticonvulsant drugs, he still suffers recurrent seizures.

Case 4

B. A., the first child of healthy, unrelated parents, was born at 37 weeks' gestation by cesarean section because of fetal distress.

Neonatal weight, length, and head circumference were below the third percentile. Spontaneous activity and muscular tone were significantly reduced at birth. Deep tendon reflexes were not elicitable.

Cerebral CT scan demonstrated a smooth cortical surface, tetraventricular hydrocephalus, corpus callosum agenesis, and cerebellar vermis hypoplasia.

Serum CK was persistently elevated (4000 U/l), EMG revealed myopathic changes, and histological examination of the muscle biopsy specimen showed a pattern typical of CMD.

Bilateral retinal hypopigmentation with an abnormal vascular pattern, small lens opacities, and remnants of tunica vasculosa lentis were found on opthalmological examination. Electroretinogram response was absent from both eyes and no cerebral response was recorded by flash visual evoked potentials.

Bilateral glaucoma requiring surgical treatment developed at the age of 5 months.

The boy is now 2 years old and shows no developmental gain. From the age of 6 months, he began to suffer from generalized seizures, initially poorly controlled by therapy. Serial EEGs showed multifocal abnormalities.

Discussion

Type II lissencephaly (agyria with or without regional pachygyria) and other brain malformations associated with eye abnormalities were first reported by Walker [25]. Warburg later confirmed these findings as part of a specific syndrome and suggested familial recurrence [26, 27].

Ocular abnormalities include retinal dysplasia, microphthalmia, posterior colobomas, persistence of fetal vascular structures, and anterior chamber malformations (cataracts, corneal clouding, cleavage defects). In addition to agyria and pachygyria, hydrocephalus, hypoaplasia of midline structures, cerebellar micropolygyria, and vermis hypoplasia, white matter hypomyelination and posterior encephaloceles may frequently be found. Subsequent reports demonstrated the coexistence of CMD in these patients and confirmed autosomal recessive inheritance [1, 3–5, 6, 9, 14–16, 18, 23, 24].

Several names have been proposed to designate this condition: HARD $\pm$ E syndrome [17], cerebro-oculo-muscular syndrome or COMS [3], cerebro-ocular dysplasia-muscular dystrophy or COD-MD [24], Walker-Warburg syndrome or WWS [5].

The association of muscular, ocular, and brain involvement has been described by Fukuyama et al. [10] and Santavuori et al. [20] in two other genetic syndromes, respectively designated as Fukuyama congenital muscular dystrophy (FCMD), and muscle, eye, and brain disease (MEBD). The former is characterized by muscular dystrophy, polymicrogyria, and/or pachygyria and hypomyelination of cerebral white matter; eye abnormalities are an uncommon feature. Patients described by Santavuori et al. show a clinical picture similar to FCMD, constantly associated with severe ocular symptoms [19].

After extensively reviewing the literature on syndromes with CMD and brain and eye malformations, Dobyns et al. [6], recently reached these conclusions: (a) the WWS phenotype includes CMD; (b) diagnostic criteria for WWS are: type II lissencephaly, typical cerebellar and retinal malformations, and CMD; (c) there are no reasons for considering WWS, COMS, and MEBD as separate entities; and (d) WWS and FCMD should be classified separately because of the less severe clinical course in FCMD, with somewhat different cerebral, cerebellar, and retinal abnormalities (prevalence of polymicrogyric as opposed to agyric changes in FCMD, absence of cerebellar vermis hypoplasia but frequent cerebellar dysplasia, absence of typical retinal dysplasia). Our opinion is that our cases fulfil the criteria proposed by Dobyns et al. [6] and may be diagnosed as WWS. Prominent data are summarized in Table 1. In our series, lissencephaly was not an isolated defect: at least two additional cerebral abnormalities (hydrocephalus, agenesis and/or hypoplasia of the septum pellucidum and corpus callosum, white matter hypodensity) were evident in patients 1 and 4.

CT scanning on patient 2 revealed a very severe hydrocephalus which precluded recognition of any other abnormality.

Cerebellar malformations consisted of vermis hypoplasia in two cases (3 and 4) and posterior fossa cyst in one case (case 1).

Typical retinal malformations were present in three cases (1, 3, and 4). In patient 2, no ophthalmological examination was performed, but microphthalmia was evident.

Muscle involvement was suspected in all patients because of the clinical findings of severe hypotonia and weakness. It was confirmed by histopathology showing evidence of CMD in three cases in which muscle biopsies were taken; dystrophin was found to be present in normal amounts and normal size in the two patients in which the test was done. All patients showed severe impairment of CNS functions and no psychomotor development.

Table 1. Clinical findings in four patients with Walker-Warburg syndrome

Abnormalities	Patient			
	1	2	3	4
CNS (brain)				
Type II lissencephaly	+	?	+	+
Hydrocephalus	+	+	+	+
Cerebellar malformations	+	?	−	+
White matter hypodensity	+	?	+	−
Midline structures hypoplasia	+	?	+	+
Typical EEG pattern	+	?	+	+
Eye				
Retinal malformations				
Retinal dysplasia	+	?	+	+
Colobomas	+	−	−	−
Persistence of fetal vascular structures	+	−	−	+
Microphthalmia	−	+	−	−
Anterior chamber malformations	−	?	−	+
Muscle				
Congenital muscular distrophy	+	?	+	+

The three children (patients 1, 3, and 4) who survived the first months of life suffered from severe epilepsy with seizures, (tonic fits and infantile spasm) developing between the 5th and 8th month of life. Seizures were very resistant to ACTH and various anticonvulsant drugs, except in patient 4, in whom control of seizures was achieved by 15 months of age. EEG was strikingly similar in cases 1 and 3, showing high-amplitude θ activity and bursts of unusually fast rhythms. Although they are not specific, these findings strongly suggest an underlying CNS malformation, i.e., lissencephaly [2, 7, 11].

Table 2 compares our patients with other series recently published by Dobyns et al. [6], Leyten et al. [16], and Santavuori et al. [21]. Patients described by Santavuori as affected by MEBD show the coexistence of cerebral, ocular, and muscular involvement, but they have quite important features which allow them to be distinguished to some extent from patients labeled as having WWS [22]. The clinical expression of MEBD is milder than that of WWS, with a longer survival. About 50% of the Finnish patients could have been almost symptomless in the first months of life, whereas a severe neuromuscular impairment is evident from birth in all patients with WWS, most of whom die within 3 years and survival into adulthood has not been reported.

As for central nervous system involvement, neuroradiological detection of type II lissencephaly is not clear in MEBD. Both autopsied cases revealed a migrational defect resembling polymicrogyria rather than type II lissencephaly [21].

Abnormal ocular findings are also different in MEBD and WWS, as recently emphasized by the Finnish authors [19]. Retinal dysplasia, colobomas, microphthalmia, and anterior chamber malformations are very rare in MEBD, whereas severe progressive myopia is constantly observed; moreover, retinal findings are usually normal at birth, but retinal atrophy can develop later and is progressive.

In conclusion, we agree with the specific diagnostic criteria for WWS established by Dobyns et al. [6] on the basis of their observations and a review of several other cases previously reported in the literature under different

Table 2. Clinical and neuroradiological data on patients with brain, eye, and muscle involvement

	Our study ($n=4$)	Leyten et al. [16] ($n=4$)	Dobyns et al. [6] ($n=21$)	Santavuori et al. [21] ($n=19$)
Type II lissencephaly	3/4	3/4	21/21	?[a]
Hydrocephalus	4/4	3/4	20/21	12/12[b]
Cerebellar malformations	3/4	4/4	20/20	11/12[b]
White mater hypodensity	2/4	1/4	11/12	7/12[b]
Midline structures hypoplasia	3/4	2/2	13/14	6/12[b]
Encephaloceles	0	3/4	5/21	0/19
Ophthalmological disorders	4/4	4/4	21/21	19/19
Profound congenital hypotonia	4/4	4/4	21/21	10/19
Congenital muscular dystrophy	3/4[c]	4/4	8/ 8	19/19
Death	2/4	2/4	16/21	4/19
Age at death	1 month–3 years	1 day–4 months	2 days–3 years	6–16 years

[a] Mycropolygyria in the two autopsied patients
[b] Cerebral CT scan performed on 12 patients
[c] Muscle biopsy was not performed in patients 2, severe hypotonia was present

names. Our impression is that MEBD represents a clinical entity which can be differentiated from WWS both in terms of clinical course and in respect to certain different elements of ocular and cerebral abnormalities.

Further clinical, neuroradiological, neuropathological, and biochemical studies are certainly necessary in patients showing evidence of cerebral, muscular, and ocular involvement in order to define their characteristics and dissimilarities better. Molecular genetic studies, in particular, have a contribution to make towards establishing whether MEBD and WWS are separate entities or different expressions of the same disease.

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