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Lethal Congenital Muscular Dystrophy in Two Sibs with Arthrogryposis Multiplex: New Entity or Variant of Cobblestone Lissencephaly Syndrome?

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Abstract

We report on two sisters of first degree cousin parents who were born with severe hypotonia, arthrogryposis multiplex congenita (AMC) and dysmorphic features consistent with the fetal akinesia/hypokinesia sequence. They needed assisted ventilation and each died at the age of 5 months. Both had type II lissencephaly (cobblestone lissencephaly) which was visualized by magnetic resonance imaging (MRI) in the proband. Ophthalmic evaluation revealed no occular malformations in either of them. Brain auditory evoked potentials (BAEP) revealed bilateral severe sensorineural hearing loss in the proband, whereas an MRI-guided open muscle biopsy of the sartorius muscle (the only remaining thigh muscle) showed features of muscular dystrophy. Immunohistochemistry revealed normal dystrophin, dystrophin-associated glycoproteins (DAG) and merosin.

Certain clinical and pathological features distinguish the disease seen in these sisters from reported isolated cases where lethal AMC was associated with brain dysplasia and from the main syndromes of congenital muscular dystrophy/cobblestone lissencephaly. Differences from the *Walker-Warburg* syndrome, which simulates it in severity, included the absence of severe hydrocephalus, normal creatine kinase (for age) and minimal (mainly periventricular) white matter abnormalities. The findings suggest either an independent entity, in the studied family, or an allelic variation of the cobblestone lissencephaly (type II lissencephaly) syndrome.

Key words

Congenital muscular dystrophy – CNS malformation – Arthrogryposis

Introduction

Congenital muscular dystrophy (CMD) encompasses a group of autosomal recessive neuromuscular disorders, characterized by hypotonia, muscle weakness presenting at birth (or within the first six months of life) and dystrophic features on muscle histology (11). Joint contractures are common and vary from talipes to severe arthrogryposis multiplex congenita (26, 32, 37).

Four subgroups of CMD have been defined on the basis of the variable involvement of the brain and eyes (9, 10). In the "classical" type the eyes are spared whereas brain involvement is either absent or only confined to white matter changes on computerized tomography (CT) or magnetic resonance imaging (MRI). The brain involvement in the other 3 types is characterized by consistent structural changes at autopsy or on imaging. Most recently (12), the term cobblestone lissencephaly has been used to encompass these changes which include agyria/pachygyria (usually combined with polymicrogyria), white matter abnormalities, enlarged ventricles, brain stem hypoplasia and cerebellar (usually vermis) hypoplasia. Whereas ocular involvement is minor and inconsistent in *Fukuyama* CMD (14, 22), muscle, eye and brain (MEB) disease is characterized by severe myopia and may also be associated with strabismus, glaucoma, lens opacity, retinal dystrophy and optic atrophy (10, 12, 24). In the *Walker-Warburg* syndrome (WWS), ocular malformations are also common (6, 9, 27) but are thought to be less severe and less consistent than in MEB disease (9, 12). There is divergence of opinion as to whether MEB disease and WWS represent variants of the same condition (6, 10, 12, 34).

Whereas several cases have been described where a lethal form of CMD manifested as arthrogryposis multiplex congenita (AMC) (26, 32, 37), those associated as well with brain or ocular abnormalities have been a rarity (31, 43). We report on the clinical and molecular pathological features of a familial CMD syndrome where two sisters presented with AMC associated with cerebral malformation but no discernible ocular malformation. We also discuss the similarities and differences from the CMD syndromes, hitherto described.

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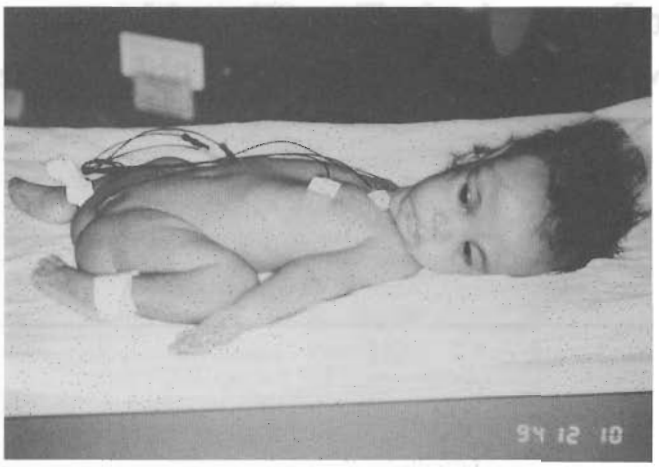

Fig. 1a

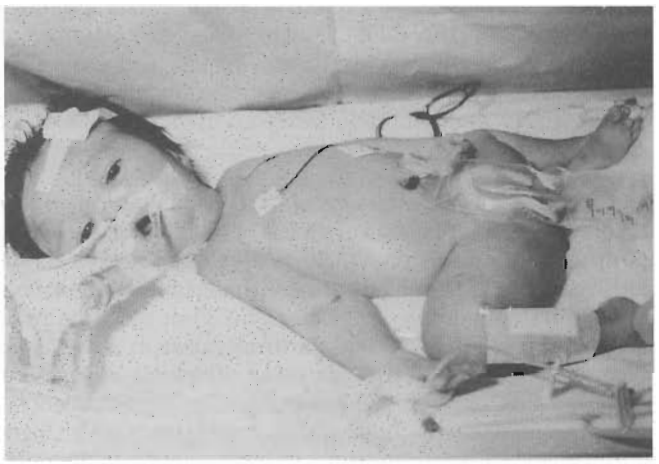

Fig. 1b

Fig. 1a and b *a)* Case 1 and *b)* Case 2: Photographs show identical dysmorphic appearance, arthrogryposis and no ocular abnormalities.

Patients and methods

Methods

Muscle samples were frozen in isopentane cooled in liquid nitrogen and stored at −80 °C. Conventional histological and histochemical techniques were performed on 10 μm thick transverse frozen cryostat sections (8). Indirect immunofluorescence microscopy of 7 μm-thick cryosections was performed as previously described (30). Monoclonal antibodies against merosin (laminin α2 chain) was purchased from GIBCO-BRL. Monoclonal antibodies against dystrophin and adhalin (α-Sarcoglycan) were previously characterized (13). Polyclonal antibodies against β-dystroglycan, syntrophins and 35 dystrophin-associated glycoprotein (35 DAG) were affinity purified from sheep antiserum against purified dystrophin glycoprotein complex as described (29). The sections were examined under a Zeiss Axioplan fluorescence microscope.

Case reports

Case 1

The proband was a female patient who was delivered normally at 38 weeks gestation following a pregnancy that was complicated by decreased fetal movements observed from 24 weeks and oligohydramnios, detected by ultrasound at 35 weeks. Apgar scores were 5 and 8 at one and 5 minutes, respectively. Birth weight was 2620 g (25th centile) and head circumference 34.0 cm (25th centile). The parents were first degree Saudi cousins. Their first pregnancy produced a girl who was alive and well at age 4 years. Their second pregnancy resulted in a girl who was similarly affected (Case 2) and died at 5 months. The paternal grandmother hat lost 3 children (one male and 2 females) during the neonatal period, but no information regarding the causes of death was available.

Examination (Fig. 1a) revealed generalized hypotonia, profound weakness and arthrogryposis involving both upper and lower limbs with fixed extension at the elbow joint and fixed flexion of both hip and knee joints. There were dysmorphic features consisting of short neck, micrognathia, high arched palate and hypertelorism. The hands were smooth with absent dermal ridges and creases, the fingers were slender and there was camptodactyly of the little finger. She had bilateral talipes equinovarus associated with prominent heels. The eyes were alert with normal ocular movements and the baby seemed, over the time, to be following and fixating on objects. Serial ophthalmological examinations revealed no abnormalities. No fasciculations were observed in the tongue. She remained completely motionless apart from occasional flexion movements of both lower limbs at the knee joints. Her breathing was mainly abdominal with minimal intercostal movements. She required ventilatory support in the first few weeks and was fed by nasogastric tube. Deep tendon reflexes were absent and sensation for crude touch and pain seemed to be intact.

Laboratory investigations showed a normal level of creatine kinase (CK) [82 U/L; N = ≤170], liver function tests (LFT), serum amino acid and urine amino acid and organic acid levels, very long chain fatty acids (VLCFA) and coagulation profile. Chromosome analysis disclosed a 46, XX karyotype. Serologically, there was no increase in antibodies against toxoplasma or a number of viruses, including rubella, cytomegalovirus, and herpes simplex (TORCH screening). No suppression burst pattern was observed in electroencephalography (EEG). Instead there was generalized slowing mainly on the right side. Brain auditory evoked potentials (BAEP) disclosed profound degree of bilateral sensorineural hearing loss. Visual evoked potentials (VEP) revealed reproducible complexes with bilaterally delayed P100 latencies, compatible with bilateral visual pathway involvement. Stimulation of the left common peroneal nerve at the knee and ankle showed no response, whereas electromyography of the left tibialis anterior revealed neither spontaneous activity nor motor unit potentials.

Computerized tomography (CT) of the brain showed mild dilatation of the lateral ventricles with a colpocephalic configuration and grade II hemorrhage in the posterior horns, small cerebellar hemispheres, hypoplasia of the posterior vermis, and diffuse low-density areas in the white matter. Cranial MRI (Fig. 2), revealed pachygyria, ventriculomegaly,

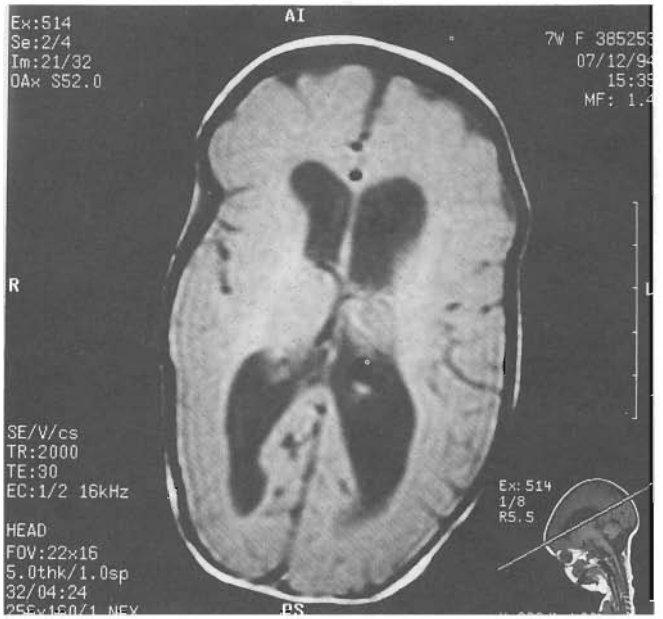

Fig. 2a

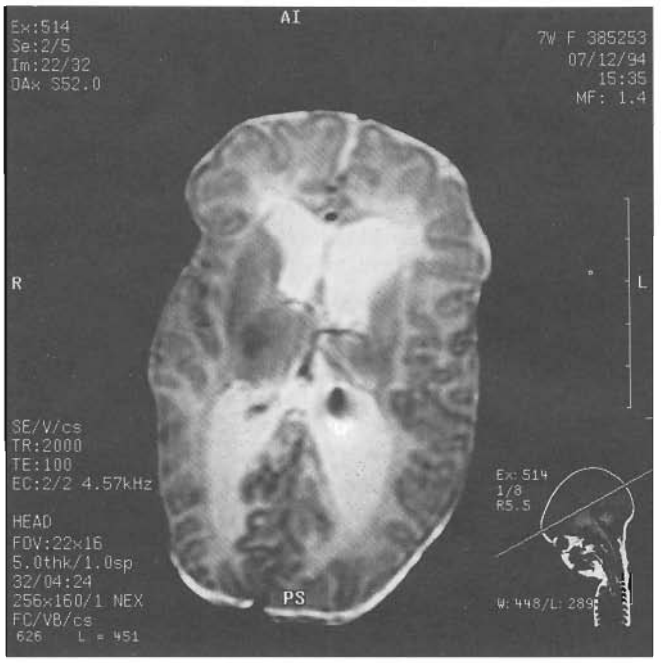

Fig. 2b

Fig. 2a and b *a)* Transverse cranial MRI image of Case 1 (spin echo [SE] 2000/30). There is pachygyria and dilatation of the lateral ventricles with a colpocephalic configuration. The small saggital image on the right hand corner shows a large posterior fossa, vermian hypoplasia and absent corpus callosum. *b)* T_2-weighted image (2000/100) SE showed mild (mainly periventricular) abnormal myelin signal.

cerebellar hypoplasia and a large posterior fossa. There was also corpus callosum dysgenesis associated with abnormal white matter signal on T_2-weighted images (mainly periventricular). Because an attempted open muscle biopsy of the left vastus lateralis failed to reveal any muscle fibres but adipofibrous tissue instead, MRI was used to locate the available

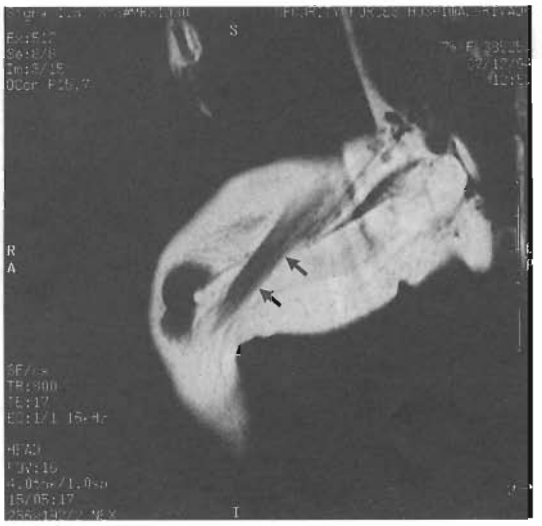

Fig. 3 MRI scan (800/17 SE) of the left thigh (Case 1) revealed the sartorius muscle (arrows) to be the only remaining muscle. Other muscles were replaced by adipofibrous tissue.

muscles in the lower limb. The only muscle preserved was the sartorius on both sides (Fig. 3) from which an open biopsy was taken.

Biopsied muscle demonstrated a dystrophic picture with variation of fibre sizes, fibre atrophy and increase in endomysial and perimysial connective tissue (Fig. 4a). Histochemical reaction revealed involvement of both fibre types and no evidence of fibre type grouping. Immunofluorescence analysis (Fig. 4b) revealed normal staining of merosin at the basal laminae surrounding each muscle fiber. Immunostaining of dystrophin and its associated proteins, including adhalin, (α-sarcoglycan), β-dystroglycan, and syntrophins was also normal.

Case 2

A female who was delivered normally at 38 weeks of gestation. Decreased fetal movements had been detected from 24 weeks of gestation, as well as polyhydramnios. Birth weight was 2630 g (25th centile), head circumference 36.0 cm (75th centile) and Apgar scores were 3 and 6 at one and 5 minutes, respectively. She had severe generalized weakness and hypotonia associated with AMC (Fig. 1b). She also showed dysmorphic features that were identical to her younger sister (Case 1). Neurologic findings were also similar. Her eyes were alert with normal ocular movements and she seemed to be capable of vision. Serial ophthalmic examinations revealed no abnormality.

Investigations showed CK of 438 U/L (N ≤170) on the first day of life and 93 U/L on day eleven. Other laboratory investigations that revealed normal results included LFT, serum and urine amino acid chromatography, VLCFA, TORCH screening and coagulation profile. Chromosomes were normal (46, XX). Cranial CT revealed brain malformations, similar to her sister (Case 1) associated with grade II hemorrhage in the posterior horns of the lateral ventricles. Electromyographic sampling of the left gastrocnemius muscle was silent and no activity was obtained; whereas nerve conduction studies of the median nerves did not show any response, either. Open muscle biopsy of the left vastus lateralis was performed;

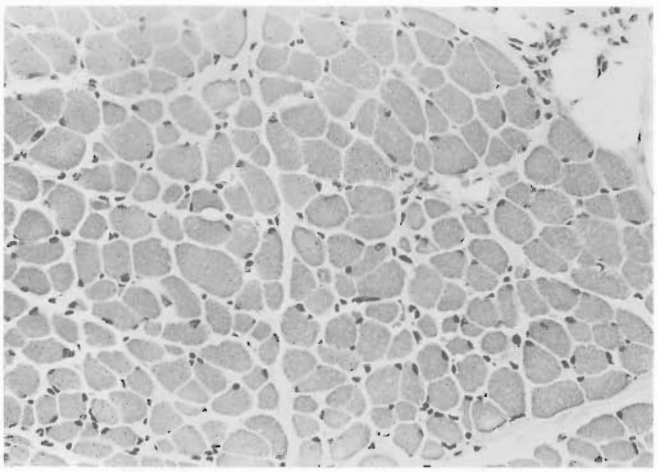

Fig. 4a

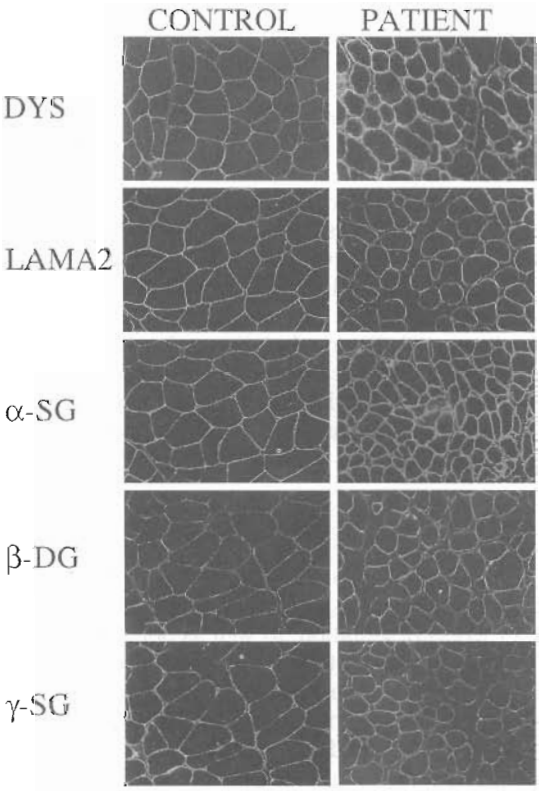

Fig. 4b

Fig. 4a and b *a)* Histology of the sartorius muscle of Case 1 showing variation in fibre sizes, atrophy of fibres and increased endomysial connective tissue (hematoxylin and eosin; original magnification x 250). *b)* Indirect immunofluorecence of the DAG components on skeletal muscle frozen sections from control and Case 1. The patient showed normal immunostaining of all the components compared to control. DYS: dystrophin; LAMA 2: laminin α2 chain; α-SG: α-sarcoglycan (adhalin); β-DG: β-dystroglycan; α-SG: γ-sarcoglycan.

but only adipofibrous tissue was seen and no muscle fibres could be identified. She required on and off ventilatory support and was fed by gavage as she was unable to suck or swallow. At the age of 5 months she died of respiratory failure.

Discussion

The common findings in the two sisters presented here include severe congenital hypotonia, profound weakness and arthrogryposis involving both upper and lower limbs with fixed extension at the elbow joints and fixed flexion of both hip and knee joints. Other dysmorphic features which both manifested such as hypertelorism, hypoplastic dermal ridges and club feet are common findings in the fetal akinesia/hypokinesia sequence in which intrinsic or extrinsic factors limit normal fetal mobility (2, 15, 16, 20). Both sisters had brain dysplasia consistent with type II lissencephaly, which was better visualized by MRI in the proband (Case 1). Type II lissencephaly is characterized by agyria/pachygyria (usually combined with polymicrogyria), white matter abnormalities (manifesting as radiolucency on CT scan or high signal on T_2-weighted MRI), enlarged ventricles (often severe enough for hydrocephalus), brain stem hypoplasia and cerebellar hypoplasia, especially involving the vermis (5, 9). This form of neuronal migration disorder characterizes WWS but has also been reported with MEB disease (24) and the *Fukuyama* type of CMD (1, 21, 36, 38).

In a recent European Neuromuscular Centre Consortium on CMD (12), it was proposed to replace Type II lissencephaly by the term "cobblestone lissencephaly" for the entire group of brain malformations observed in WWS, MEB disease and *Fukuyama* CMD. On the other hand, both siblings had alert eyes and ocular movements were preserved. Ophthalmic evaluation revealed no dysplastic lesions (e.g. microphthalmia, corneal opacities, glaucoma or cataract) and the fundi and retinae appeared normal. Neurophysiological studies (confined to VEP in Case 1) revealed delayed latencies, consistent with visual pathway involvement and possibly reflecting the associated brain malformation.

Open muscle biopsy revealed the dystrophic nature of the disease in Case 1, but only after being guided by MRI which revealed the sartorius to be the only remaining thigh muscle. We propose that the MRI becomes part of the work-up for cases of AMC to guide the muscle biopsy procedure. An unguided muscle biopsy (as in Case 2) might only reveal adipofibrous tissue, making the distinction been neurogenic and dystrophic causes hardly tenable.

Selective muscle involvement, particularly within the components of the quadriceps femoris of patients with CMD, has been reported (40), and the mechanism responsible for it could be related to the embryological development of the muscle (17). On the other hand, the posture of the lower limbs in both sisters (i.e. hip flexion and abduction associated with knee flexion) is compatible with the functional anatomy of the sartorius muscle, the only remaining muscle in the thigh (28). The rest have been converted to fibroadipose tissue as revealed by the unguided muscle biopsies and the MRI image (3, 40).

Molecular pathological examination in Case 1 revealed normal dystrophin and dystrophin-associated glycoproteins (DAG) including merosin (laminin α2). It is noteworthy that merosin deficiency was detected in a sub-group of cases manifesting the "classical" form of CMD (39), whereas a partial merosin deficiency was found in the *Fukuyama* type (17). In contrast, merosin expression at the skeletal muscle was consistently preserved in cases of WWS (42).

Table 1 Comparison of phenotypic findings in the present cases with the described congenital muscular dystrophy (CMD)/brain anomaly syndromes*.

	Present report						
	Case 1	Case 2	MEBD	WWS	*Fukuyama* CMD	*Olive* et al case [31]	*Wargowiski* et al case [43]
Age at presentation	B	B	B–6 mo	B	< 8 mo	B	B
Age at death	5 mo	5 mo	< 1y–18 y	< 1y–34 y	1–27 y	2 d	3 d
Inheritance	AR	AR	AR	AR	AR	?	?
Cobblestone lissencephaly	+	+	+	+	+	–	–
Eye abnormalities							
– severe myopia	?	?	Consistent	R	R	?	?
– microphthalmia	–	–	R	R	–	–	–
– corneal opacity	–	–	R	R	–	–	–
– glaucoma	–	–	R	R	–	NR	NR
– lens opacity	–	–	R	R	R	–	+
– retinal malformation	–	–	Consistent	Consistent	–	NR	–
– optic atrophy	–	–	R	R	R	NR	–

* Based on references 1, 4–6, 9, 10, 12, 14, 19, 21–23, 31, 35, 41–43

+, present; –, absent; ?, unknown

Abbreviations: AR: autosomal recessive; B: birth; CMD: congenital muscular dystrophy; d: days; MEBD: muscle, eye and brain disease; mo: months; NR: not reported; R: reported; WWS: *Walker-Warburg* syndrome; y: year

Table 1 summarizes the clinical and pathological features observed in the two sisters with the currently recognized CMD/brain anomaly syndromes (10, 12). Comparison is also made with other cases of AMC reported to be associated with brain malformation. The severity of the condition, its early lethality and the normal merosin immunostaining serve to differentiate it from the *Fukuyama* CMD. The brain malformation observed in the two sisters is similar to the MEB disease and WWS where the full expression of cobblestone lissencephaly had been observed in most patients, especially on MRI scan (5, 12, 24). However, neither of the two sisters manifested the eye malformations reported in MEB disease or WWS (6, 9, 10, 12, 24, 27). They also showed no clinical evidence of retinal dysplasia, being a consistent finding in MEB disease and WWS (6, 12, 35). However, no ERG was done in the present patients to rule out sub-clinical retinal involvement.

On the other hand, the disease in our patients simulates the course of WWS rather than MEB disease. Whereas a significant proportion of WWS cases are stillborn or survive for a mean age of only 4 months (Median = 9 months), MEB disease patients develop spasticity around 5 years of age and die between 6 and 16 years (6, 34). However, certain features seem to differentiate it from the WWS. These are the absence of severe hydrocephalus which is usually progressive in WWS and the normal CK, which is extremely unusual in the latter condition (34). Also the white matter abnormalities are more dramatic in WWS and include absent white matter interdigitations, edema and sometimes cystic changes (6, 33). Whereas BAEP revealed severe bilateral sensorineural hearing loss in Case 1, the reported auditory pathway involvement in cases of WWS included poorly formed wave V on BAEP suggesting midbrain dysfunction in one case (45) and microtia with absent auditory canals and conductive hearing loss in another patient (25).

Two other isolated cases (31, 43) simulated the sisters described in this report in the severity of CMD, since both were born with AMC and died early in infancy. The patient reported by *Wargowski* et al (43) had lens opacity whereas the case of *Olive* et al (31) had no discernible ocular abnormalities similar to our patients. Features of lissencephaly were absent in these cases.

It is noteworthy that both sisters described in the present report showed identical phenotype to each other. This is compatible with previous observations that among the familial cases of CMD/brain malformation syndromes there is more variability between families than between affected sibs (4, 6, 14, 19, 23, 41). Whether they will prove to be independent entities or allelic variation of the "cobblestone lissencephaly" syndrome remains to be resolved by linkage studies of the individual disorders.

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