Cobblestone-like brain dysgenesis and altered glycosylation in congenital cutis laxa, Debré type
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ABSTRACT

Objective: To delineate a new syndrome of brain dysgenesis and cutis laxa based on the description of 11 patients belonging to nine unrelated families recruited through an international collaboration effort.

Methods: Careful clinical assessment of patients from birth to the age of 23 years with follow-up studies ranging from 3 to 20 years. Biochemical studies of serum proteins glycosylation by isoelectric focusing and capillary zone electrophoresis were performed in 10 patients. Brain MRI studies using conventional methods were analyzed in eight patients.

Results: An expanded clinical spectrum of a syndrome comprising facial dysmorphia (enlarged anterior fontanelles, downward slant of palpebral fissures, prominent root of the nose), a connective tissue disorder (inguinal hernia, hip dislocation, high myopia), and neurologic impairment was defined. Early developmental delay was followed by onset of generalized seizures by the end of the first decade and a subsequent neurodegenerative course. A defect of N- or N- plus O-glycosylation of serum transferrins and ApoCIII was observed in 10 patients. An unusual cobblestone-like cortical malformation over the frontal and parietal regions was seen in eight patients and cerebellar abnormalities, including two patients with Dandy-Walker malformation, were observed in three patients.

Conclusions: Our results suggest that autosomal recessive cutis laxa, Debré type, initially considered a dermatologic syndrome, is a multisystemic disorder with cobblestone-like brain dysgenesis manifesting as developmental delay and an epileptic neurodegenerative syndrome. It might represent a metabolic cause of Dandy-Walker malformation. It is associated with a deficient N- and O-glycosylation of proteins and shares many similarities with muscle-eye-brain syndromes.

Neurology® 2008;71:1602–1608

GLOSSARY

ARCL = autosomal recessive congenital cutis laxa; CZE = capillary zone electrophoresis; DWM = Dandy-Walker malformation; FCMD = Fukuyama congenital muscular dystrophy; IEF = isoelectric focusing; MEB = muscle-eye-brain disease; WWS = Walker-Warburg syndrome.

Autosomal recessive congenital cutis laxa (ARCL) represents a heterogeneous group of disorders characterized by redundant skin present from birth. Although dominant inheritance has been described (OMIM 123700), autosomal recessive inheritance is more common, with two distinct subtypes described that differ at the ultrastructural level.

The pulmonary emphysema type of ARCL (ARCL type 1, OMIM 219100) is characterized by fragmentation of elastic fibers, which are present as unassembled primary components. The Debré type (ARCL type 2, OMIM 219200) is characterized by developmental
delay, large anterior fontanelle, facial dysmorphia, and a paucity of elastic fibers on skin biopsy. ARCL is rare, with fewer than 40 patients with the pulmonary emphysema type and fewer than 50 with the Debré type reported (appendix e-1 on the Neurology® Web site at www.neurology.org). A few other patients have had variant or unspecified phenotypes (appendix e-1). In the pulmonary emphysema subtype, homozygous mutations of EGF-containing fibulin-like extracellular matrix protein 2 (EFEMP2) and both homozygous and heterozygous mutations of Fibulin-5 (FBLN5) have been reported, the latter blurring the distinction between autosomal dominant and recessive forms.1-4 Mutations in the elastin (ELN) gene have been reported in six families with autosomal dominant cutis laxa associated with variable aortic aneurisms or pulmonary emphysema.5-9 Recently, a Dutch group described N- and O-linked glycosylation defects in three patients with autosomal recessive cutis laxa and developmental delay.10

We recently established an international collaboration to further delineate the phenotype and map the causative genes. Here we describe an additional 11 patients from nine families with Debré type ARCL and further delineate the brain and neurologic features.

METHODS Clinical reports. Patient 1. This girl was born to unrelated Belgian parents after a pregnancy complicated by
The skin abnormalities are always most prominent in newborns (A, patient 1), then become less marked but still evident at older ages (B, patient 2 at 8 years; C, patient 11 at 23 years).

In Débré type autosomal recessive congenital cutis laxa, the wrinkles or skin folds are narrow and shallow, especially in comparison to the skin folds in the pulmonary emphysema type.
showed an abnormal pattern consistent with congenital disorder of glycosylation type 2 (CDG2) with an increase of trisialo- and disialotransferrin (figure 4, B and C). IEF of serum ApoCIII was analyzed in patients 6 and 7 and in their parents. Both affected children showed a clearly lower disialo ApoCIII band than their parents, pointing to hyposialylation (figure 4D). No serum was available from the parents of the other patients, precluding firm conclusions about their ApoCIII patterns.

DISCUSSION Among these 11 patients with Debré type ARCL, we found a recognizable pattern of abnormalities involving facial appearance, connective tissue structures especially the skin, and brain. The most consistent craniofacial abnormalities consisted of an abnormally large anterior fontanelle, prominent supraorbital ridges and nasal root, telecanthus, and downsloping palpebral fissures (figure 1). The skin phenotype was characteristic of cutis laxa with generalized overfolding and wrinkling, but no hyperelasticity as seen in Ehlers-Danlos syndrome. In contrast to the pulmonary emphysema type of ARCL, furrows in the skin are tightly spaced (figure 2). Most patients had abundant coarse hair, and other features indicating a more generalized connective tissue dysplasia such as high myopia or dislocated hips. Skin biopsies supported the diagnosis, showing reduced number and fragmentation of elastin fibers (data not shown). A trend toward improvement of cutis laxa throughout childhood was seen.

All patients had moderately delayed developmental milestones and mental retardation with good social interactions, although special education was required. Generalized seizures began between 6 and 12 years in all patients but one, and were often intractable. The severe seizures probably contributed to shortened survival, with death in childhood occurring in two children reported in the literature and four from our series, all by 17 years. Several patients, especially patient 11 and her two affected sibs, had a progressive course from early childhood characterized by dementia, spasticity, ataxia, and hearing loss that led to death by 9 and 11 years in the two sibs and a bedridden state in patient 11 by 16 years. This distinct clinical course probably correlates with the cerebral atrophy observed on brain imaging.

Brain imaging demonstrated a recurrent pattern of dysgenesis consisting of a cortical malformation in all but one patient, and variable microcephaly and cerebellar hypoplasia (figure 3 and figures e-1 and e-2). The cortical malformation involves the posterior frontal, perisylvian, and parietal regions, and was seen in all but one child. The abnormal cortex partly resembles polymicrogyria, except that the cortical ribbon appears smooth in some areas and irregular in others (see figure e-1), which explains why the cortical malformation has been variably interpreted as pachygyria or polymicrogyria in different patients. Midline sagittal and lower axial images show cerebellar vermis (v) hypoplasia in patients 1-3. This appears as mild hypoplasia of the posterior vermis in patient 1 (A), and as typical Dandy-Walker malformation with small and upwardly rotated vermis, cystic dilatation of the 4th ventricle, and enlarged posterior fossa in patients 2 (D, E) and 3 (G, H).
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<th>3</th>
<th>4</th>
<th>5</th>
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</table>

OFC = occipito-frontal circumference; MR = mental retardation; BMR = Bruch membrane rupture; HM = high myopia; CD = corneal dystrophy; IEF = isoelectric focusing; CDG2 = IEF consistent with CDG type 2; ApoCIII = apolipoprotein-CIII; MIC = microcephaly at age of evaluation and not necessarily at birth; COB = cobblestone-like cortical malformation; HCC = hypoplasia (partial agenesis) of the corpus callosum; HYD = hydrocephalus; V-R = prominent perivascular (Virchow-Robin) spaces in central white matter; ATR = atrophy of both cerebrum and cerebellum; CVH = cerebellar vermis hypoplasia; DWM = Dandy-Walker malformation.
The cortical malformation seen in eight of our patients resembles the striking cobblestone cortical malformation seen in Walker-Warburg syndrome (WWS), muscle-eye-brain disease (MEB), and Fukuyama congenital muscular dystrophy (FCMD). In these syndromes, the gyral pattern varies from smooth to irregular, and on autopsy the cortex is very disorganized with neurons and glia mixed with fibroblasts and blood vessels in superficial regions.\textsuperscript{18-20} The malformation results from defects in the basal lamina (pial limiting membrane) that allow inappropriate migration of neurons and glia into the subarachnoid space to form extensive marginal gli-neuronal heterotopia.\textsuperscript{21,22} These syndromes are associated with mutations in six genes that encode known or putative O-linked glycosyltransferases: \textit{FCMD}, \textit{FKRP}, \textit{LARGE}, \textit{POMGnT1}, \textit{POMT1}, and \textit{POMT2}.\textsuperscript{23-28} The encoded proteins are involved in synthesis of alpha-mannosyl side chains of alpha-dystroglycan, which bind to the extracellular matrix protein laminin in retina, brain, and muscle.\textsuperscript{29-31} However, glycosylation of ApoCIII is normal in serum because ApoCIII is synthesized in the liver and apparently not released into the circulation.

The cortical malformation seen in our patients also resembles the malformation seen in two other autosomal recessive syndromes. The first of these is so-called bilateral frontal-parietal polymicrogyria associated with mutations of \textit{GPR56}.\textsuperscript{32-34} Based on a brain imaging appearance that closely resembles MEB, one of the authors first reported this syndrome as “cobblestone lissencephaly with normal eyes and muscle” in 1996.\textsuperscript{35} Other authors described the same malformation alternatively as pachygria\textsuperscript{36} or polymicrogyria.\textsuperscript{33,34,37} Interestingly, the GPR56 protein is heavily glycosylated.\textsuperscript{38} The brain imaging appearance also resembles the CEDNIK syndrome caused by mutations in SNAP29.\textsuperscript{39} We suggest using the term frontal predominant or frontoparietal cobblestone-like cortical malformation for these disorders. We hypothesize that the brain malformations observed in Debré type ARCL and these other disorders share a common pathogenesis.

In further support of this analysis, mutations in the a2 subunit of the V-type H\textsuperscript{+}-ATPase (\textit{ATP6V0A2}) were recently identified in all our patients except for patient 2.\textsuperscript{40}

\textbf{REFERENCES}

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