

# Cerebroretinal Microangiopathy With Calcifications and Cysts (CRMCC)

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Received 23 May 2007; Accepted 16 August 2007

Extensive intracranial calcifications and leukoencephalopathy are seen in both Coats plus and leukoencephalopathy with calcifications and cysts (LCC; Labrune syndrome). Coats plus syndrome is additionally characterized by the presence of bilateral retinal telangiectasia and exudates while LCC shows the progressive formation of parenchymal brain cysts. Despite these apparently distinguishing features, recent evidence suggests that Coats plus and LCC represent the same clinical entity with a common primary pathogenesis involving a small vessel obliterative microangiopathy. Here, we describe eight previously

unreported cases, and present an update on one of the original Coats plus patients to highlight the emerging core clinical features of the "cerebroretinal microangiopathy with calcification and cysts" (CRMCC) phenotype. © 2007 Wiley-Liss, Inc.

**Key words:** intracranial calcification; leukodystrophy; intracerebral cysts; leukoencephalopathy with calcifications and cysts; exudative retinopathy; Coats; Labrune

**How to cite this article:** Briggs TA, Abdel-Salam GMH, Balicki M, Baxter P, Bertini E, Bishop N, Browne BH, Chitayat D, Chong WK, Eid MM, Halliday W, Hughes I, Klusmann-Koy A, Kurian M, Nischal KK, Rice GI, Stephenson JBP, Surtees R, Talbot JF, Tehrani NN, Tolmie JL, Toomes C, van der Knaap MS, Crow YJ. 2008. Cerebroretinal microangiopathy with calcifications and cysts (CRMCC). *Am J Med Genet Part A* 146A:182–190.

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DOI 10.1002/ajmg.a.32080

## INTRODUCTION

In 1988, Tolmie and co-workers reported on two sisters with bilateral Coats disease (retinal telangiectasia and retinal exudates), intracranial calcification, sparse hair, and dystrophic nails. Subsequently, we documented skeletal defects with a tendency to fractures, a mixed cerebellar and extrapyramidal movement disorder and a leukodystrophy in this same condition which we termed Coats plus syndrome [Crow et al., 2003].

In 1996, three cases with a leukoencephalopathy and extensive calcifications of the basal ganglia, cerebellar grey nuclei, and white matter were described by Labrune et al. [1996]. These patients also had progressive intracerebral cysts but no retinal abnormalities. A subsequent report by Nagae-Poetscher et al. [2004] described three additional children with leukoencephalopathy, calcification, and cysts (LCC; Labrune syndrome) where one child also demonstrated Coats-like retinal changes, thus suggesting that LCC and Coats plus might be pathogenetically related. More recently still, Linnankivi et al. [2006] reported four further such overlap cases confirming the link between these two disorders.

Here, we describe eight previously unreported cases, and provide an update on one of the original Coats plus patients, to highlight the emerging core clinical features of the “cerebroretinal microangiopathy with calcifications and cysts” (CRMCC) phenotype. These cases illustrate the variability of the disease and its progressive nature which includes a tendency to life-threatening gastrointestinal bleeding. Notably, Coats plus, LCC, and CRMCC do not have an OMIM entry, and we suspect that these phenotypes are under-recognized.

## CLINICAL REPORTS

### Patient 1

This female was born to unrelated Caucasian parents. She had an affected brother (Patient 2) and two further healthy siblings. She was born at term

with a birth weight of 2.1 kg (<0.4th centile) and an OFC on the 3rd centile. She developed normally until 1 year of age when she was noted to have a right-sided hemiplegia and she experienced focal seizures affecting the right side. CT revealed extensive intracranial calcification (Fig. 1A,B) and decreased signal in the occipital white matter indicating white matter disease. Metabolic, immunological, and infective investigations were normal.

At age 18 months she was walking independently and had several words. At 2 years of age she developed a left divergent squint. Fundoscopy revealed a left choroidoretinal scar and macular exudates consistent with bilateral Coats disease. At this time she started to lose skills and by 2 years and 6 months she could no longer walk or talk although she remained bright. Subsequently, she developed a generalized dystonia with a torticollis and bradykinesia which made walking impossible. By age 10 years, due to oropharyngeal spasticity, she was unable to protect her airway and a percutaneous gastrostomy was inserted. A year later she had lost completely the use of her limbs, was wheelchair bound, and fully dependent. Her skin and nails were normal and she had no history of fractures. At 13 years of age she developed pneumonia and died.

### Patient 2

This brother to Patient 1 was born at term weighing 2.31 kg (<0.4th centile). His early development was unremarkable although from the age of 2 years he was considered to have a reduced attention span. At 3 years of age he developed an acute encephalopathy and was treated with acyclovir and steroids. A cranial CT scan demonstrated extensive intracranial calcification and MRI showed patchy white matter change (Fig. 2A). Fundoscopy revealed an exudative retinopathy consistent with bilateral Coats disease which, despite extensive laser treatment, progressed so that he lost the sight in his right eye.

He made a good recovery from his acute encephalopathy and remained well without any focal

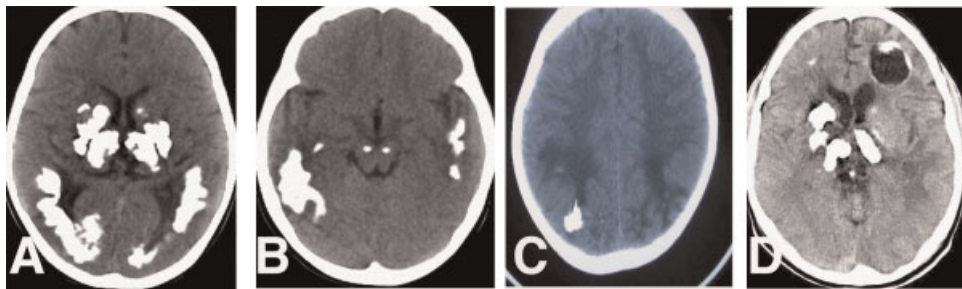


FIG. 1. CT scans showing variable and asymmetric calcification which can involve the white matter, basal ganglia, midbrain, and cerebellum. Calcification of the pons and cerebellum can also be seen (not shown here). Hypodensity of the white matter is evident in some images. A large intraparenchymal cyst in the left frontal region is present in Patient 8. [A,B: Patient 1 at 1 year; C: Patient 3 at 12 years; D: Patient 8 at 26 years]. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

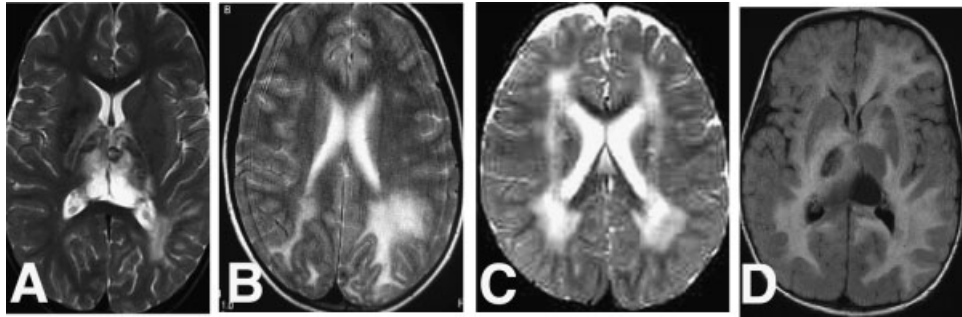


FIG. 2. MRI scans demonstrating variable and patchy signal abnormality in the thalamus, internal capsule, and white matter. A cystic mass is present in the right thalamus and another in the splenium of the corpus callosum of Patient 9 (D). [A: Patient 2 at 3 years; B: Patient 3 at 12 years; C: Patient 7 at 3 years; D: Patient 9 at 9 months].

neurological signs until 5 years of age. At that time he developed a left-sided hemidystonia with hyper-reflexia and his speech deteriorated with features of a stutter and dysarthria. By 11 years of age his dystonia has progressed so that walking was extremely difficult. He had reduced understanding and concentration.

### Patient 3

This 15-year-old Caucasian male was born to non-consanguineous parents at term weighing 2.59 kg (0.4th centile). Early milestones were normal but at 18 months of age a tremor of the left arm was noted. Between the ages of 6 and 11 years he experienced eight fractures of both long and short bones following minimal trauma. He had generalized low bone mass with an age-matched Z score of  $-2.4$ . He was diagnosed with osteogenesis imperfecta and started on pamidronate.

At 9 years of age, without any previous awareness of a visual deficit, he failed a school eye examination. Further investigation revealed a bilateral exudative retinopathy consistent with Coats disease (Fig. 3). Both parents underwent fluorescein angiography and his mother was considered to have a subtle peripheral leakage possibly consistent with an exudative hyaloretinopathy although funduscopy, visual acuity, and a cranial CT were all normal.

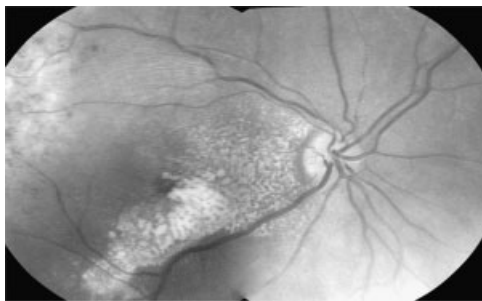


FIG. 3. Patient 3: Right eye; heavy exudate in macular area with telangiectasia temporally, before treatment.

At the age of 12 years, neurological examination demonstrated a left-sided tremor and hyper-reflexia in all four limbs. Cranial CT revealed widespread calcification and hypodensity of the parieto-occipital white matter (Fig. 1C) with white matter signal abnormalities also seen on MRI (Fig. 2B).

At 13 years of age he developed a normocytic, normochromic anemia without obvious cause. On examination there were no skin, hair, or nail abnormalities. He was 157 cm tall (50th–75th centile) and weighed 40.6 kg (25th–50th centile). He was intellectually intact and performing averagely at school.

### Patient 4

This Egyptian boy was born to non-consanguineous parents at term with reported low-birth weight. He was presented at 6 years of age with visual difficulties when funduscopy revealed bilateral macular exudates consistent with Coats disease. He had sparse fair hair with bitemporal graying and dystrophic nails but no abnormal skin pigmentation. He also had a small penis with an atrophic right testis and an undetectable testis on the left. Neurological examination was normal and IQ was 79 on the Wechsler scale. A CT scan of his brain demonstrated intracranial calcification involving the thalamus and white matter and hypodensity of the parieto-occipital white matter. A skeletal survey revealed mild osteopenia. He had a normal male karyotype. However, chromosomal breakage studies showed an excess of breaks with diepoxybutane, although not as high as seen in Fanconi anemia.

At 8 years of age he remains below the 0.4th centile for all growth parameters. He does not exhibit any neurological signs. There is no history of bleeding although repeated blood examinations have demonstrated a hypochromic, microcytic anemia.

### Patient 5

Clinical details of this female, and her younger sister, born to non-consanguineous Scottish parents

have been published previously [McGettrick and Loeffler, 1987; Tolmie et al., 1988; Crow et al., 2003]. To summarize, there was intrauterine growth retardation (IUGR) but early development was normal. She developed bilateral Coats disease at 3 years of age and underwent enucleation of the left eye. Vision was retained in the right eye, although signs of an early cataract were seen at the age of 20 years. She also showed sparse hypopigmented hair, which began graying in her teens, dysplastic nails, and transparent skin. She had an extensive intracranial calcification in the cerebrum, cerebellum, and basal ganglia and MRI demonstrated a leukodystrophy. At age 13 years a skeletal survey revealed diffusely osteopenic bones and sclerotic and lytic changes of the femoral metaphyses. She had normal intellect and studied law at college. The patient had negative molecular testing of *VHL*, *DKC1*, and *LMNA* considering possible phenotypic variants of Von Hippel-Lindau syndrome (OMIM: 193300), dyskeratosis congenita (OMIM: 305000), and lamin A/C disease (OMIM 150330).

At age 22 years she gave birth to a female child without any significant maternal health problems. The infant has multiple medical difficulties relating to prematurity but has no signs of Coats disease or intracranial calcification at 3 years of age.

At 23 years of age the patient presented with diarrhea and frank rectal bleeding and hemoglobin of 3.9 g/dl. She was peripherally edematous and had ascities. Endoscopy revealed esophageal varices and histology of the upper and lower gastrointestinal tract showed large telangiectatic mucosal blood vessels. In addition, she was considered to have chronic liver disease and portal hypertension.

### Patient 6

This female was the second child born to third cousins of Anglo-Irish ancestry. An ultrasound scan at 32 weeks demonstrated IUGR with oligohydramnios so that an emergency caesarean was performed. Her birth weight was 0.812 kg (<0.4th centile) and OFC 26.5 cm (0.4th–2nd centile). A cranial ultrasound on day 2 of life revealed

bilateral, small echogenic calcified foci in the frontal regions and the thalami. She was slow to establish feeding and was finally discharged home on day 54 of life tolerating breast feeds. At this time her height and weight were below the 0.4th centile and her OFC on the 2nd–9th centile.

Ophthalmological examination on day 54 of life revealed abnormal retinal vascularization and pre-retinal hemorrhages peripherally and over the macula of the left eye. There was incomplete vascularization of the right retina extending as far as zone I. After a period of few months, exudates were seen in the right eye. A clinical diagnosis of retinopathy of prematurity was made. Despite bilateral laser treatment followed by vitrectomies she experienced bilateral retinal detachments with scarring and was left with light perception only in both eyes.

In view of central hypotonia and peripheral hypertonia, a diagnosis of cerebral palsy was made at age 7 months. At 13 months of age she developed short-lasting, jerky movements of the arms and legs. An EEG demonstrated focal epileptiform activity over the left superior frontal, central, and posterior temporal regions. Cranial MRI revealed features of a non-progressive hydrocephalus with a narrowed aqueduct and small fourth ventricle as well as widespread abnormalities of the white matter in the frontal lobes and periventricularly. Brain CT showed extensive calcification of the periventricular, thalamic, basal ganglia, and dentate regions (Fig. 4).

She continued to fail to thrive and at the age of 21 months her weight was 5.76 kg and length 66.4 cm, both below the 3rd centile. At 3 years of age she was noted to have a generalized osteopenia with a reduction of her bone density to 49% of expected and multiple compression fractures of the thoraco-lumbar vertebrae with loss of height and anterior wedging.

At 3 years 2 months of age she presented with recurrent melena and hematemesis. Endoscopic biopsy demonstrated duodenitis and dilated gastric and duodenal veins. Abdominal ultrasound showed portal hypertension with para-umbilical and gastrohepatic varices. A liver biopsy revealed portal fibrosis with abnormally large vascular channels but

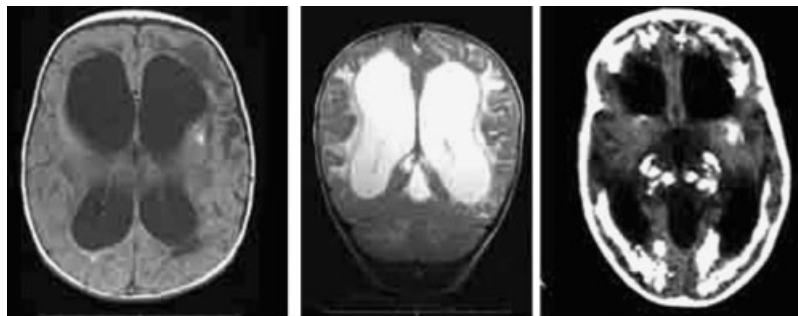


FIG. 4. Patient 6: MRI showing features of a non-progressive hydrocephalus and extensive abnormalities of the white matter. Additionally, CT (right) reveals widespread calcifications.

without established cirrhosis. She had a normal alkaline phosphatase with a minimal elevation of transaminases and normal bleeding indices. Metabolic, biochemical, immunological, infective, and chromosomal studies were non-contributory. Stomach and small bowel biopsies showed multiple foci of superficial ulceration suggestive of ischemic injury involving the antrum and proximal jejunum. The microvasculature demonstrated dilated channels with many abnormal arterioles traversing the muscularis mucosae into the lamina propria. These vascular anomalies were suggestive of an underlying telangiectasia. A Whipple's procedure with J-tube insertion and left gastric artery embolization was performed in an attempt to control the gastro-intestinal hemorrhage. However, her liver function continued to deteriorate and she died aged 3 years 9 months.

At autopsy the brain was small (815 g). Three subpial cysts (1 cm × 2 cm) were obvious at the level of the midbrain and upper pons (Fig. 5A). The gross anatomy was unremarkable. Coronal sections showed significant tissue loss in both the white and gray matter, but particularly the white matter where periventricular, subcortical cysts had formed (Fig. 5B). The tissue loss was associated with ventriculomegaly, thinning of the cortical mantle, and marked thinning of the corpus callosum. There were large areas of intracerebral and ventricular hemorrhage and extensive parenchymal calcification with sparing only of the medulla and spinal cord. Calcification was especially prominent at the gray–white matter junction although in some areas there was pan-cortical involvement. Numerous telangiectatic vessels of variable size and mural thickness were seen in the pons, midbrain, cerebellum, diencephalon, cerebral cortex, and the eyes (Fig. 6). These vessels were also frequently

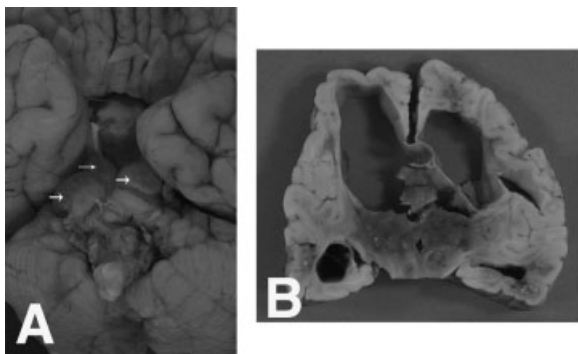


FIG. 5. Patient 6: Autopsy examination of the brain demonstrating the presence of three subpial cysts associated with the upper pons and midbrain (A). A coronal slice of the cerebral hemispheres, at the level of the thalami, shows dramatic loss of cerebral white matter and associated hydrocephalus ex vacuo. Each lateral ventricle is bordered by a paraventricular cyst (right larger than left). The remaining white matter contains multiple foci of calcification and this appears to be most prevalent at the gray–white junction. The thalami are discolored and in addition to multiple foci of calcification, show multiple brownish dots and linear profiles which represent the abnormal vasculature (B).

thickened, sclerotic, and sometimes calcified. Examination of the eyes showed sclerotic and thrombosed vessels bilaterally with marked optic nerve atrophy, gliosis, and reactive changes consistent with longstanding retinal detachment. The bones were generally osteopenic with a hypocellular trilineage bone marrow. Considering a possible diagnosis of Aicardi-Goutieres syndrome (MIM: 225750) mutation analysis of *TREX1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* was undertaken and was normal.

### Patient 7

This 3-year-old girl is the first child of healthy, unrelated Dutch parents. Birth weight was 1.75 kg (2nd–9th), length 39 cm (<0.4th), and head circumference was 30 cm (9th centile). Due to motor asymmetry and concerns over her development, a cranial CT was obtained at the age of 3 months, which revealed focal calcified deposits in the basal ganglia, thalami, and cerebral white matter. No additional abnormalities were seen on MRI of the brain with the cerebral white matter considered normal for her age. Ophthalmologic examination was unremarkable. The subsequent 2 years were dominated by insufficient intake with frequent vomiting and poor growth for which no specific cause was found. Her development was delayed. She walked without support at the age of 3 years and could not speak at this time. Auditory investigations revealed normal hearing. Her height remained < 0.4th centile with a normal head circumference. She had gray-blond, sparse hair, and deep-set eyes. She had a divergent strabismus but ophthalmologic examination was otherwise normal. Tendon reflexes were hyperactive but her plantars were downgoing. Karyotype was normal and extensive metabolic investigations were unremarkable. CSF analysis, including interferon alpha assay, revealed no abnormalities. PCR for CMV DNA on her Guthrie card was negative. Repeat CT scan revealed an increase in number and size of the calcium deposits at the cortical-white matter interface and in the cerebral white matter, basal ganglia, and thalami. MRI of the brain revealed extensive cerebral white matter abnormalities (Fig. 2C). EM of a skin biopsy showed no evidence of a vasculopathy. Endocrine studies were normal.

### Patient 8

This male patient was the third child of healthy, unrelated Dutch parents. His birth weight was 3.3 kg (9th–25th). He presented with gait problems at the age of 8 years when neurological examination revealed a mild right-sided hemiparesis. CT of the brain showed extensive calcifications in the cerebellum, basal ganglia, and cerebral white matter. Ophthalmologic examination was unremarkable. At the age of 10 years he displayed signs of elevated intracranial

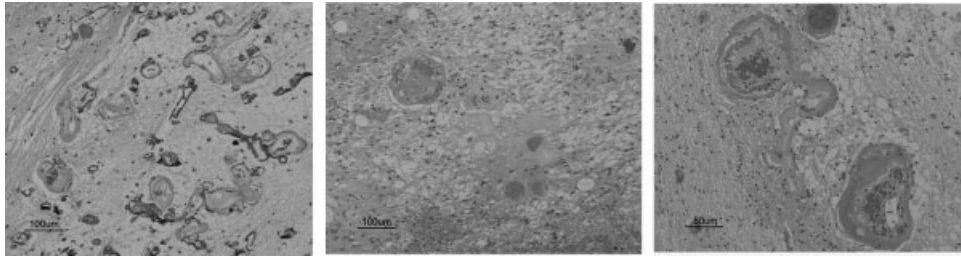


FIG. 6. Patient 6: Microscopic examination of the basal ganglia (**left**), periventricular white matter (**middle**), and right eye (**right**) revealing thickened, sclerotic, and sometimes calcified and thrombosed vessels.

pressure. MRI of the brain showed large intraventricular cysts, mainly in the area of the third ventricle, and extensive white matter signal abnormalities. Parts of the walls of the cysts were surgically removed for drainage and this procedure was repeated at age 12 years. Over time, he experienced slow motor and cognitive decline.

At the age of 26 years, physical examination revealed normal height, weight, and head circumference. Again, fundoscopy was unremarkable and eye movements were normal. He had a pseudobulbar palsy with facial signs of Parkinsonism and asymmetric cogwheel rigidity of the arms. He had myoclonus of the right arm and leg. He had a position and intention tremor of the arms but no resting tremor. Power and sensory functions were intact. His tone was increased in upper and lower limbs and reflexes were asymmetrically exaggerated with bilateral extensor plantar responses. He had a slow, spastic-ataxic gait. MRI revealed extensive cerebral white matter abnormalities and large intraparenchymal cysts in the left frontal region with smaller cysts in the basal ganglia, right cerebellar hemisphere, and third ventricle. After contrast, enhancement of the walls of the cysts was seen. CT showed extensive calcium deposits in the dentate nucleus, thalamus, basal ganglia, and cyst walls (Fig. 1D).

### Patient 9

This 18-month-old boy was the 3rd child of consanguineous Somali parents. He was born at term weighing 2.8 kg (9th centile) and with an OFC of 33.6 cm (9th centile). On day 5 he was admitted to the neonatal unit with jittery movements. An infection screen was negative and an EEG was normal. However, cranial ultrasound demonstrated echogenic cerebral parenchyma with slit-like ventricles.

He was readmitted at age 7 weeks with focal seizures. A cranial CT scan showed patchy increased density in the right thalamus thought to represent previous hemorrhage. His seizures settled on phenobarbital, developmental and neurological examination was normal, and he was discharged home after 5 days. At 9 months he was growing along the 9th

centile, exhibited a marked right hand preference, and was noted to have 13 cafe au lait patches. An MRI brain showed extensive signal abnormality in the white matter of both cerebral and cerebellar hemispheres. Additionally, a cystic mass in the right thalamus and another in the splenium of the corpus callosum prompted discussion with a neurosurgeon (Fig. 2D). Brain CT revealed multiple foci of dense calcification throughout the white matter and in the caudate and dentate nuclei as well as diffuse white matter hypodensity.

Ophthalmologic review at 11 and 16 months was normal. At 16 months he was cruising and using a few single words. Lower limb reflexes were symmetrically brisk. At this time he fractured his skull with no recallable trauma. A skull X-ray showed a “copper beaten” appearance but a skeletal survey was otherwise normal. All other investigations, including a karyotype and metabolic studies, were unremarkable (Table I).

### DISCUSSION

We describe nine cases with progressive cerebral calcifications and leukoencephalopathy. Patients 1–6 show features consistent with Coats plus syndrome. Patient 7 has similar features with IUGR, intracranial calcification, white matter changes, and ectodermal involvement although she does not demonstrate any retinal abnormalities at the age of 3 years. Patients 8 and 9 have intracerebral cysts as previously described in LCC. Of note, Patient 6 had both an exudative retinopathy and cystic masses at the level of the midbrain and upper pons identified at autopsy. Such overlap cases were similarly described by Nagae-Poetscher et al. [2004] and Linnankivi et al. [2006], thus suggesting that Coats plus and LCC are manifestations of the same disease spectrum termed “cerebroretinal microangiopathy with calcifications and cysts” (CRMCC) by Linnankivi and co-workers [2006].

Key diagnostic handles of this eye, brain, bone, and gut phenotype include pre- and post-natal growth retardation, bilateral retinal telangiectasia and retinal exudates, intracranial calcification, a leukodystrophy sometimes associated with parenchymal brain cysts,

TABLE I. Summary of Features Seen in Patients 1–9

Disease manifestation	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Exudative retinopathy	+	+	+	+	+	+	–	–	–
Intracerebral calcification	+	+	+	+	+	+	+	+	+
Cranial cysts	–	–	–	–	–	+	–	+	+
Leukoencephalopathy	+	+	+	+	+	+	+	+	+
IUGR (born < 10th centile)	+	+	+	+	+	+	+	–	+
Spasticity	+	–	–	–	–	+	+	+	+
Ataxia	–	–	–	–	+	–	–	+	–
Dystonia	+	+	+	–	+	–	+	+	–
Epilepsy	+	–	–	–	–	+	–	–	+
GI hemorrhage	–	–	–	–	+	+	–	–	–
Osteopenia/fractures	–	–	+	+	+	+	–	–	+
Skin/nail involvement	–	–	–	+	+	–	+	–	+
Anemia	–	–	+	+	–	–	–	–	–
Genital abnormalities	–	–	–	+	–	–	–	–	–

osteopenia and a tendency to fractures, bone marrow suppression, and gastrointestinal bleeding with cirrhosis. Less frequently, patients demonstrate sparse, graying hair, dystrophic nails, and café au lait patches. Many patients experience progression of their neurological disease with spasticity, dystonia, ataxia, and cognitive decline. Additionally, the risk of significant gastrointestinal involvement with bleeding and liver failure appears to be high. The clinical phenotype of CRMCC is thus wide and variable; affected individuals may present to specialists in neonatology, ophthalmology, developmental pediatrics, bone metabolism, gastroenterology, and pediatric neurology and not all features of the condition are necessarily seen in every patient. Considering reports of affected sibling pairs and the presence of consanguinity in some families, it is likely that CRMCC is inherited as an autosomal recessive trait.

Revesz et al. [1992] reported a male with IUGR, bilateral exudative retinopathy, sparse hair, hyperpigmentation, intracerebral calcification, and cerebellar hypoplasia that developed aplastic anemia and died of bone marrow failure aged 19 months. Similar cases were also described by Mills et al., 1979; Duprey and Steger, 1988; Kajtar and Mehes, 1994; Niedermayer et al., 2000; Gayatri et al., 2002. Interestingly, as in Patient 4 presented here, the last three reports documented an increased frequency of chromosome breaks, suggesting a possible overlap with Fanconi anemia. Two of our patients (3 and 4) have an unexplained anemia and 6 of the 13 cases reported by Linnankivi et al. [2006] required repeated blood transfusions from the second decade of life due to a persistent hypochromic anemia. It seems likely then that bone marrow suppression, sometimes progressing to frank aplastic anemia, is part of the CRMCC phenotype and that Revesz syndrome (MIM 268130) is the same, or an allelic variant.

The neuroimaging findings of these cases appear to be distinctive. The pattern is that of bilateral and asymmetrical dense plaques of calcification centered on the thalamus, basal ganglia, and subcortical white matter with a leukodystrophy evident on MRI or

CT which can show enhancement after contrast [Linnankivi et al., 2006]. Brainstem involvement is also noted. In many cases there were extensive changes on a background of relatively little cerebral atrophy. Calcification may be seen soon after birth (Patients 6, 7, and 9) but this feature can also develop at a later age. It is of note that significant calcification can occur in the absence of neurological features (Patient 4). The pattern of calcification and white matter involvement seen in CRMCC is distinct from that observed in Aicardi-Goutières syndrome [Lanzi et al., 2005], cytomegalovirus [Boppa et al., 1997], Cockayne syndrome [Sugita et al., 1992], HERNs [Jen et al., 1997], CADASIL [van den Boom et al., 2003], SPENCD syndrome [Renella et al., 2006], and the heterogeneous Fahr disease [Oliveira et al., 2004] while other features of these conditions also allow for their differentiation from CRMCC.

Patient 6 illustrates an extreme and early presentation of CRMCC with gastro-intestinal bleeding and liver failure resulting in death by age 3 years. Liver biopsy revealed portal fibrosis with abnormally large vascular channels but without established cirrhosis and there were features suggestive of telangiectasia in the small bowel. Six patients in the series of Linnankivi et al. [2006] also experienced severe and recurrent gastrointestinal bleeding and abnormalities of the gastrointestinal vasculature with thick-walled and dilated vessels were recorded in two patients. Additionally, two affected individuals developed hepatic insufficiency and esophageal varices. Similar features were present in four cases reported by van Effenterre et al. [1989].

Four of the patients we report had documented osteopenia and Patient 3 experienced particularly severe bone involvement with multiple fractures which prompted a clinical diagnosis of osteogenesis imperfecta. Similarly, Sazgar et al. [2002] described osteopenia, intracranial calcification, exudative retinopathy, IUGR, graying hair, and café au lait patches in a male sib-pair and one further patient that we previously reported [Crow et al., 2003] experienced pathological fractures secondary to osteopenia.

Again, six of seven patients examined radiologically in the series reported by Linnankivi et al. [2006] had osteopenia and two patients suffered pathological fractures so that we consider bone involvement in CRMCC as a major diagnostic feature.

On neuropathological examination in Patient 6, numerous telangiectatic vessels of variable size with thickened, sclerotic and calcified walls were observed in the pons, midbrain, cerebellum, and cerebral cortex. Additionally, cystic masses were seen bilaterally at the level of the midbrain. Linnankivi et al. [2006] documented similar proliferation of the small vessels in the brain with thickened, hyalinized, and calcified vessel walls in six patients. Thus, at least with regard to the central nervous system involvement, it seems appropriate to consider CRMCC as an obliterative microangiopathy. In the eye, retinal telangiectasia and exudates might result from occlusion of the microvasculature or may occur due to incomplete vascularization of the retina during development. Interestingly, *FZD4*, *LRP5*, and *NDP* are components of the Wnt-signaling pathway involved in retinal vascular development and mutations in these genes are associated with eye phenotypes, including familial exudative vitreoretinopathy (FEVR) [Robitaille et al., 2002; Toomes et al., 2004], pseudoglioma in osteoporosis pseudoglioma syndrome [Gong et al., 2001], Norrie disease [Black et al., 1999], and retinopathy of prematurity (ROP) [MacDonald et al., 2005] reminiscent of the features are seen in CRMCC. It is of further note that mutations in *LRP5* are also associated with abnormalities of bone mass and a tendency to fracture [Gong et al., 2001; Downey et al., 2006]. Consequently, we speculate that mutations in these same genes, or other genes involved in the Wnt-signaling pathway, may be responsible for the CRMCC phenotype.

### ACKNOWLEDGMENTS

We would like to dedicate this paper to the memory of Professor Robert Surtees, who died during the preparation of the manuscript. We would like to thank the patients and their families for their cooperation in the preparation of this manuscript.

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