

Cerebroretinal microangiopathy with calcifications and cysts

A case report

Wenrui Xu, MD^a, Jiuliang Zhao, MD, PhD^b, Yicheng Zhu, MD, PhD^c, Weihong Zhang, MD, PhD^{a,*}

Abstract

Rational: Cerebroretinal microangiopathy with calcifications and cysts (CRMCC) is believed to be an autosomal recessive genetic disease, with disorders in multisystem organs. Its characteristic neurological disorders manifested on neuroimaging are a triad of leukoencephalopathy, intracranial calcifications, and parenchymal cysts. In this paper, we report a CRMCC patient with multisystem involvement, focusing on the neuroimaging features, to get a better understanding of the rare disease and improve our diagnostic ability.

Patient Concerns: The 23-year-old female patient firstly presented with an adolescence onset of ophthalmological manifestations. Four years later, hematological and neurological disorders occurred, the latter of which demonstrated a relatively slow progression in the following 7 years preceding her presentation to our hospital.

Interventions: During hospitalization, disorders involving digestive, cardiovascular and respiratory systems were also detected. In addition, a more comprehensive depiction of neurological disorders on neuroimaging was also obtained.

Diagnoses: On the basis of multiple system disorders and the detection of mutations in conserved telomere maintenance component 1 (CTC1) gene, a diagnosis of CRMCC was made.

Outcomes: After supportive therapy during her 4-week hospitalization, the patient's general condition improved and was released from the hospital.

Lessons: CRMCC could be primarily diagnosed with the aid of its multiple system disorders and remarkable neuroimaging features. Cerebral micro hemorrhages determined by the combination of CT and T2^{*}-weighted magnetic resonance images in our case could provide some additional information for diagnosis. Furthermore, several other associated disorders were depicted for the first time in our case, expanding the clinical spectrum of CRMCC.

Abbreviations: ALD = adrenoleukodystrophy, CRMCC = cerebroretinal microangiopathy with calcifications and cysts, CSF = cerebrospinal fluid, CT = computed tomography, CTC1 = conserved telomere maintenance component 1, EEG = electroencephalogram, H1-MRS = proton magnetic resonance spectroscopy, HRCT = high-resolution CT, LCC = leukoencephalopathy with cerebral calcifications and cysts, MRI = magnetic resonance images, MS = multiple sclerosis.

Keywords: case report, cerebral calcification, cerebroretinal microangiopathy with calcifications and cysts, inherited diseases, leukoencephalopathy

1. Introduction

Cerebroretinal microangiopathy with calcifications and cysts (CRMCC) is believed to be an autosomal recessive genetic disorder, with an onset age ranging from infancy to adolescence.^[1–3] So far, only 15 cases have been reported in

the English literature.^[3–11] It is a multisystem disease and clinical phenotypes are variable, among which the neurological disorder manifested on neuroimaging is the most remarkable feature of CRMCC: a triad of leukoencephalopathy, intracranial calcifications, and parenchymal cysts.^[4–6,8,9] In this paper, we report a

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^a Department of Radiology, ^b Department of Rheumatology, ^c Department of Neurology, Peking Union Medical College Hospital (PUMCH), Peking Union Medical College and Chinese Academy of Medical Sciences (PUMC&CAMS), Beijing, People's Republic of China.

* Correspondence: Weihong Zhang, Department of Radiology, Peking Union Medical College Hospital (PUMCH), Peking Union Medical College and Chinese Academy of Medical Sciences (PUMC&CAMS), Beijing, People's Republic of China (e-mail: zhangweihong@pumch.cn).

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23-year-old female patient with CRMCC, who has a long history of multisystem involvement for 11 years, with focus on the neuroimaging features, to get a better understanding of the rare disease and improve our diagnostic ability.

2. Case presentation

A 23-year-old female patient was admitted to our hospital with a long history of multisystem disorders for 11 years. The patient was found an impaired vision in a routine physical examination at 12 years of age and diagnosed as “retinal venous vasculitis.” Laser treatment and steroid were then prescribed and she improved slightly. Four years later, she began to have a pallor complexion, gingival bleeding, and a decline in memory. Splenectomy was then performed at local hospital according to the diagnosis of “microcytic hypochromic anemia”; however, no obvious effect was observed. In the meanwhile, the patient also experienced her first convulsive seizure in her right lower limbs after awakening from sleep, without loss of consciousness.

In the following 7 years preceding this presentation, the neurological symptoms progressed to convulsive seizure in all the limbs after dizziness and diplopia, with loss of relevant memory occasionally, along with a higher frequency. During this episode, the patient was highly suspected of CRMCC by a neurologist; however, biopsy of brain was prevented by a low platelet count of $50 \times 10^9/L$ (normal range: $100\text{--}300 \times 10^9/L$) at that time. Other symptoms remained stable.

On admission, relevant physical and auxiliary examinations were conducted and the main results were demonstrated as follows.

Neurological examinations demonstrated that the patient experienced a mild decline in calculating, memorizing, understanding, orienting and language expressing, as well as hyper-reflexia in bilateral lower limbs and right-sided Babinski positivity. Neuroimaging including cranial computed tomography (CT) and magnetic resonance images (MRI) revealed a variety of intracranial calcifications which involved the thalamus, basal ganglia, parietal lobe, temporal lobe, occipital lobe, and cerebellum (Fig. 1A–D), 3 parenchymal cysts located in the left

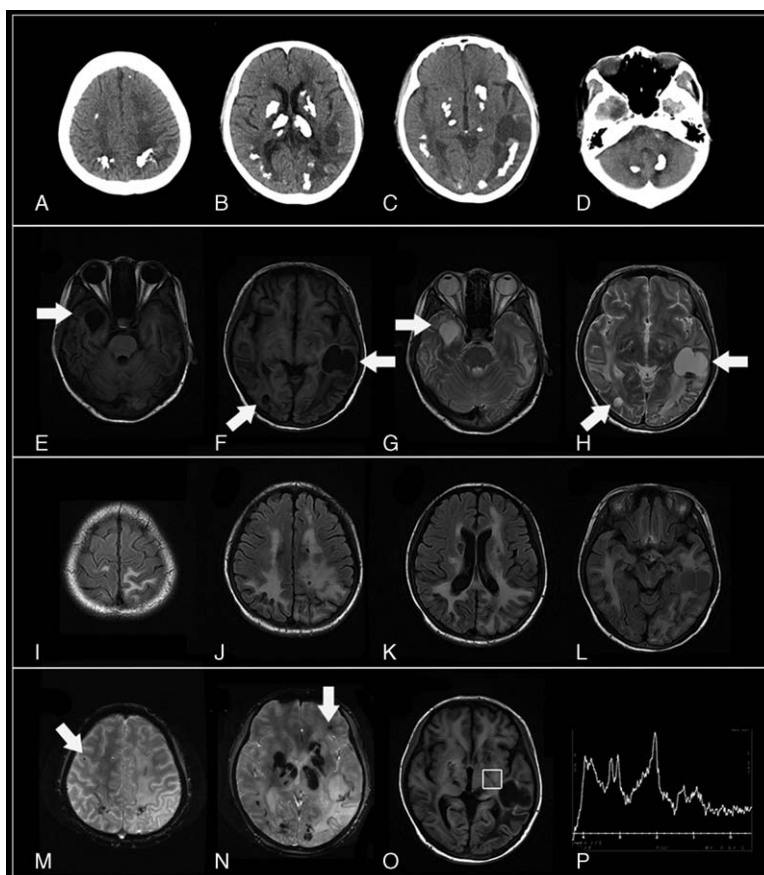


Figure 1. (A–D) Axial CT images demonstrated multiple calcifications within bilateral thalamus, basal ganglia, subcortical white matter of parietal, temporal and occipital lobe, and dentate nucleus of cerebellum, an intraparenchymal cyst in the left temporo-parietal region and widespread low-density area of the cerebral white matter. (E–P) MRI of the brain was performed using a 1.5T scanner (Signa EXCITE, GE Medical Systems, Pewaukee, WI) with the following sequences: T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), fluid-attenuated inversion recovery image (FLAIR), diffusion-weighted image (DWI), and gradient-echo imaging (T2*WI). (E–H) T1WI (repetition time/echo time (TR/TE), 1538.8/9.128 ms; field of view (FOV), 24 cm; and matrix size, 32×32) and T2WI (TR/TE, 3620/88.884 ms; FOV, 24 cm; and matrix size, 32×32) showed multiple cysts in the left temporo-occipital lobe, right temporal lobe, and right occipital lobe. (I–K) FLAIR (TR/TE, 8002/166.132 ms; FOV, 24 cm; and matrix size, 32×32) images depicted the diffuse hyperintense area in cerebral white matter. In addition, some abnormalities, which were suggestive of calcifications and cysts, could also be observed. (M, N) T2*WI (TR/TE, 300/20 ms; FOV, 24 cm; and matrix size, 32×32) revealed several hypointense regions within the thalamus, basal ganglia, subcortical white matter in bilateral parietal, temporal and occipital lobes representing calcifications (in combination with A–D) and micro hemorrhages (white arrow). (O–P) Single-voxel proton magnetic resonance spectroscopy analysis (H1-MRS, TR/TE, 1500/35 mms; FOV, 24 cm; matrix size, 32×32 ; and 14.4 cm^3 voxel size) on the left basal ganglia revealed a normal spectrum. DWI = diffusion-weighted image, FLAIR = fluid-attenuated inversion recovery image, FOV = field of view, H1-MRS = proton magnetic resonance spectroscopy, MRI = magnetic resonance imaging.

temporo-occipital lobe, right temporal lobe, and right occipital lobe, respectively (Fig. 1E–H), diffuse hyperintense region in cerebral white matter (Fig. 1I–L), and micro hemorrhages within the left temporal lobe and right occipital lobe (Fig. 1M and N). Single-voxel proton magnetic resonance spectroscopy (H1-MRS) analysis on the left basal ganglia revealed a normal spectrum (Fig. 1O and P). Scalp electroencephalogram (EEG) showed continuously released low-high amplitudes at the left parieto-occipital area and postmedian temporal area with epileptiform activity. Both the routine cerebrospinal fluid (CSF) and biochemical analysis showed normal results.

Fundoscopy by an ophthalmologist demonstrated bilateral obsolete cerebroretinal microangiopathy.

Laboratory blood examination and bone marrow aspiration confirmed the diagnosis of microcytic hypochromic anemia, with hemoglobin of 39 g/L.

Disorders involving digestive system, which were revealed by ultrasonography and contrast-enhanced CT of the abdomen, include cirrhosis, thickening of the wall of gallbladder, portal hypertension and ascites. In addition, on the second day of hospitalization, the patient had a symptom of fever, diarrhea, and gastrointestinal bleeding, which was obviously alleviated after probiotics and anti-infective therapy.

Cardiovascular disorders of the patient demonstrated by physical examination and echocardiography include hypertension (159/104 mm Hg), chronic heart failure (NYHA III), and pericardial effusions. Edema of lower extremities and proteinuria also occurred in our patient, which were highly suspected to result from hypertension, according to the dramatic improvement after medication for hypertension.

Despite that the patient experienced no apparent respiratory symptoms, a thoracic high-resolution CT (HRCT) scan was performed in order to exclude suspected pulmonary infection. To our surprise, the HRCT revealed the thickening of bronchovascular bundles and bilateral pleural effusions.

On the basis of all the manifestations demonstrated above and the detection of mutations in conserved telomere maintenance component 1 (CTC1) gene, a diagnosis of CRMCC was made. After supportive therapy during her 4-week hospitalization, the patient's general condition improved and was released from the hospital.

No special family history was found.

3. Discussion

Coats' plus is a pleiotropic disorder mainly characterized by retinal telangiectasia and exudates (Coats' disease), intracranial calcifications, and leukoencephalopathy, without the formation of parenchymal cysts.^[12,13] Other disorders affecting the bone, liver, and gastrointestinal tract may also coexist.^[12,13] However, leukoencephalopathy with cerebral calcifications and cysts (LCC) is a rare neurological disorder consisting of these 3 radiographic findings, without extra-neurological findings.^[14,15] In 2004, Nagae-Poetscher et al^[4] reported the first case with overlap characteristics of Coats' plus and LCC, featuring by bilateral retinal telangiectasia and exudates, leukoencephalopathy, intracranial calcifications, and parenchymal cysts for neurological disorders. In 2006, Linnankivi et al^[5] proposed the concept of CRMCC referring to this syndrome and postulated that Coats' plus and LCC were manifestations of the same disease spectrum of CRMCC. In recent years, mutations in the CTC1 gene were detected in both Coats' plus and CRMCC.^[1,13] However, according to the negative results of mutation in CTC1 gene

screening in patients with LCC, Livingston et al^[16] proposed that LCC was a purely neurological disorder distinct from Coats' plus and CRMCC.

Our patient's characteristic neuroimaging, multisystem involvement and the detection of mutations in CTC1 gene allowed us to make a firm diagnosis of CRMCC in spite of the absence of brain biopsy. As reported in previous studies, in addition to the characteristic visual and neurological manifestations, patients with CRMCC may also exhibit other disorders, including cirrhosis, portal hypertension, gastrointestinal bleeding, anemia and thrombopenia with varying degrees of bone-marrow suppression, and skeletal changes.^[4,5,8,9,11,17]

Our patient had an early onset of 13 years of age with an impaired vision and exhibited a relatively slow progression. Microcytic hypochromic anemia, temp thrombopenia, cirrhosis and portal hypertension occurred in our patient as previously described in the literature^[4,5]; however, bone marrow suppression was not evident on the results of bone marrow puncture. In addition, the endoscopic examination was prevented by the patient's poor condition and inability to cooperate; therefore, we were not sure whether it was gastro-intestinal telangiectasia, or infection that caused her gastro-intestinal bleeding during hospitalization. No obvious skeletal disorders were observed except for an old fracture in the left eighth anterior rib, which was caused by a sudden falling resulted from a convulsive seizure, according to her relatives. What confused us were the unexplained cardiovascular disorders (hypertension, chronic heart failure, and pericardial effusion) and the asymptomatic respiratory abnormalities demonstrated by thoracic HRCT scans (the thickening of bronchovascular bundles and bilateral pleural effusions).

In addition to the multiple system disorders, neuroimaging features of CRMCC should also be highly addressed. Furthermore, differential diagnosis emphasizing on neuroimaging may also encompass many diseases regarding intracranial calcifications, parenchymal cysts, and leukoencephalopathy on neuroimaging.

In contrast with the 8 previously reported CRMCC patients with neuroimaging materials available in their articles,^[2–7,9,11] our case provided a more comprehensive view of its neuroimaging features. In our case, multiple intracranial calcifications were best depicted on CT images. The parenchymal cysts and leukoencephalopathy were clearly demonstrated on MR images, which were acquired with different sequences. Notably, we first reported the micro hemorrhages detected by the combination of CT and T2*-weighted images. This finding indirectly supported the hypothesis that obliterative angiopathy involving small vessels might be the pathogenesis in both retinal and neurological disorders in CRMCC.^[2,4–6] Therefore, gradient-echo imaging (T2*-weighted imaging or susceptibility weighted imaging), which was used for detecting cerebral micro hemorrhages, may be an essential tool for diagnosis. In contrast with the only 1 reported CRMCC patients with H1-MRS data available, which revealed minimal increase in the choline peak, mild decrease in the N-acetylaspartate peak, and a lactate peak,^[10] our patient showed a normal spectrum. This may result from the different voxel location.

For differential diagnosis, parenchymal neurocysticercosis was the first to be considered on the basis of intracranial calcifications and parenchymal cysts on neuroimaging. However, in parenchymal neurocysticercosis, extensive leukoencephalopathy is merely seen.^[18] In addition, both the CSF and biochemical analysis of our patient showed normal results. Parenchymal tuberculosis may also exhibit multiple cysts, perilesional edema, and

calcifications on neuroimaging; however, the extensive leukoencephalopathy and the negative results of acid-fast bacteria stains, smear, and culture of CSF excluded this diagnosis.^[19]

Intracranial symmetric calcifications within bilateral thalamus, basal ganglia, subcortical cerebral white matter, and dentate nucleus may appear in Fahr's disease and idiopathic hypoparathyroidism.^[20,21] However, multiple parenchymal cysts and extensive leukoencephalopathy in our patient were not supportive of these 2 entities.^[20,21] Also, the depositing of cerebral calcifications in our patient manifested relatively asymmetric compared with Fahr's disease and idiopathic hypoparathyroidism.^[20,21]

Extensive leukoencephalopathy may exist in many neurological disorders, such as multiple sclerosis (MS) and adrenoleukodystrophy (ALD).^[22,23] However, both of the 2 diseases were scarcely found to combine with cysts and calcifications, and usually exhibited characteristic lesion appearance and distribution. In MS, multiple focal ovoid lesions oriented perpendicular to the long axis of lateral ventricles appear as hypo- and hyperintense areas on T1- and T2-weighted MR images, respectively.^[22] As for ALD, the characteristic neuroimaging finding is the hyperintense "butterfly" pattern on T2-weighted images, which consisted of bilateral symmetrical leukoencephalopathy in the posterior periventricular white matter and the affected corpus callosum splenium.^[23] However, in our patient, leukoencephalopathy was extensive and asymmetric, predominantly affecting subcortical and periventricular white matter, which was inconsistent with the diseases demonstrated above.

4. Conclusion

In conclusion, we reported a CRMCC patient with multisystem involvement, with a focus on the neuroimaging features. A better knowledge of the characteristic manifestations on neuroimaging of CRMCC (a triad of leukoencephalopathy, intracranial calcifications, and parenchymal cysts) may improve our diagnostic ability of the rare entity. Parenchymal microhemorrhages determined by the combination of CT and T2*-weighted images could provide additional information and be an essential tool for diagnosis. In the meanwhile, several other associated disorders were depicted for the first time in our case, expanding the clinical spectrum of CRMCC. Further studies emphasizing on the genetic pathogenesis of the multisystem disease are still needed.

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