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# Unintentional Drowning Associated with Multiple Cerebral Cavernous Malformations

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**Abstract** Cerebral cavernous malformations (CCMs), which occur in a sporadic or familial form, can predispose a person to seizures, focal neurological impairment, and hemorrhage. Upon discovery floating in a swimming pool, a 3-year-old boy was unresponsive and not breathing, but he achieved uneventful recovery after adequate cardiopulmonary resuscitation. Diagnostic head magnetic resonance imaging confirmed multiple CCMs. Absence of affected family members was indicative of the sporadic form. Subsequently, he developed social communication deficits and restricted and repetitive behaviors, suggestive of autism spectrum disorders (ASD). Comorbidity of CCMs and ASD is rare. Seizure associated with multiple CCMs might precipitate unintentional drowning.

***Keywords:*** *autism spectrum disorders, magnetic resonance imaging, seizure, Tanaka–Binet Intelligence Quotient*

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## 1. Introduction

Cerebral cavernous malformations (CCMs; OMIM#116860) are known to be associated with structural epileptic seizures and epilepsy [1]. Most patients with CCMs remain asymptomatic, with lesions often discovered incidentally during magnetic resonance imaging (MRI) [1]. Early diagnosis of CCMs is extremely difficult especially before the appearance of neurological symptoms. Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by persistent deficits in social communication and interaction and by restrictive, repetitive patterns of behavior [2].

We herein report a Japanese boy who had experienced drowning, probably associated with multiple CCMs or ASD.

## 2. Case Report

A 3 year and 9 month old boy enjoyed attending swimming class. During one session, he was found floating in a supine position in the deep end of the pool. The instructor noticed the incident and pulled him up out of the water immediately. Upon rescue, he was pale, unresponsive and not breathing. Giving bystander cardiopulmonary resuscitation, he spewed water out and his breathing promptly recovered. After a few more artificial respiration iterations, he burst out crying and regained consciousness. He had neither febrile convulsions nor seizures. He was transferred to our hospital by ambulance.

Upon arrival, his Glasgow scale was (E3V4M6) 13. He was slightly pale and drowsy. Chest auscultation was normal. Neither the liver nor spleen was enlarged. Peripheral oxygen saturation was 94% on air. Vital signs consisted respectively of 106/61 mmHg blood pressure, 123 beats/min pulse, of 36.4°C temperature, and 30 beats/min respiration. Blood gas analysis showed 7.34 pH, 42 mmHg $PaCO_2$, 71 mmHg $PaO_2$, 22 mmol/L $HCO_3^-$, and -3.3 mmol/L base excess. Chest X-ray showed bilateral faint pulmonary infiltrates. Laboratory results were 0 mg/dl C-reactive protein, 109 mg/dl blood sugar, 11.1 mg/dl blood urea, 0.28 mg/dl serum creatinine, 132.4 mEq/L sodium, 3.17 mEq/L potassium, 99.3 mEq/L chloride, 9.4 mg/dL calcium, 3.9 mg/dL phosphate, and 100 U/L creatinine kinase. The white blood cell count was 10,600/μL. Hemoglobin was 12.3 g/dL. The electrocardiogram was normal.

After admission, he vomited water repeatedly. No fever or seizure developed. He was discharged on the following day. Diagnostic electroencephalography (EEG) and head MRI were performed 5 days after discharge. Results of EEG showed no epileptic discharge. Head MRI confirmed multiple CCMs (Figure 1). No family member had epilepsy or CCM. He had no cutaneous venous malformations. He has been followed up at Toyama University Hospital. We found nothing remarkable about this boy.

At 4 years and 11 months, he tended to lag a bit behind his daycare peers. He felt some difficulty in understanding

communications and in having conversations. His intelligence score using Tanaka–Binet Intelligence Quotient was borderline at 76 (chronological age, 5 years and 2 months; mental age, 3 years and 11 months). His language comprehension was also slightly low. Furthermore, his tendencies to need some time to adapt to new places or situations, being selective, doing things at his own pace, and preferring to play alone were compatible with a diagnosis of ASD. He began to attend a child development support center. He was subsequently lost to follow up.

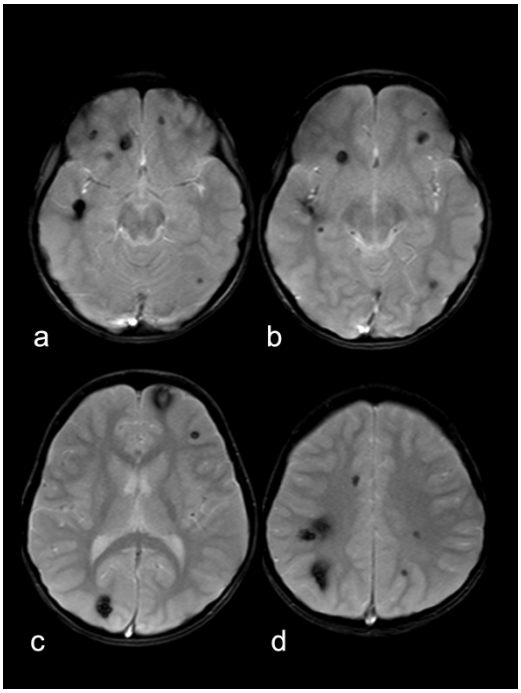


**Figure 1.** a–d: Axial T2-star weighted, fast field echo images show multiple cerebral cavernous malformations in cerebral hemispheres

## 3. Discussion

We report two important clinical findings. Seizure associated with CCMs might precipitate unintentional drowning. Comorbidity of CCMs and ASD is rare.

Accidental drowning might be precipitated by a CCM-associated seizure. Unfortunately, nobody saw the instant of his drowning, leaving open the question of whether he had actually had a seizure, or not. Seizures are a second major presenting symptom of CCMs after hemorrhage in children [1]. Seizures are common in people with ASD [3]. Both neurodevelopmental disorders and seizures are higher risk factors for drowning, especially in children [4]. Normal interictal EEG did not exclude epilepsy [5]. He must have had a seizure associated with CCMs or ASD because any seizure potentially impedes awareness and disturbs fine motor control [4].

Second, comorbidity of CCMs and ASD is rare. Felix et al. reported rapid eye movement sleep behavior disorder associated with CCMs [6]. López et al. reported microdeletion syndrome including dysmorphic features, CCMs, and hyperglycemia [7]. Tordjman et al. described comorbid ASD and Williams–Beuren syndrome (WBS) caused by 7q11.23 deletion [8]. Our patient showed no WBS; *CCM1* gene was located at 7q21 [1]. To date, at least three genes of *CCM1-3* were identified in CCMs, none of which were putative ASD genes [1,9]. The structural MRI findings in young children with ASD are abnormally increased total brain volume, which was not applicable to our patient [10]. It is noteworthy that a Medline survey revealed no report of CCMs comorbid with ASD. Co-occurrence of CCMs and ASD might be merely coincidental in our patient.

Actually, CCMs arise sporadically and are hereditary. Absence of known clinically affected family members is suggestive of sporadic form. Sporadic cases with multiple lesions might get familial mutations from asymptomatic parents and might show *de novo* mutation [1]. To confirm the familial type and mutation, genetic analysis was applied, as mandatory in this case.

## 4. Conclusions

Seizure associated with multiple CCMs or ASD might precipitate unintentional drowning. Association between CCMs and ASD is rare. A genetic workup should be scheduled to clarify the familial form and the responsible mutation.

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