

# Systemic Capillary Leak Syndrome With Cerebral Involvement in a *C9orf72* Expansion Carrier

## Case Report and Review of the Literature

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## Abstract

### Objective

Systemic capillary leak syndrome (SCLS) is a rare condition associated with episodes of hypotension, hemoconcentration, hypoalbuminemia, and rhabdomyolysis. We describe a middle-aged man presenting with several distinct SCLS-like episodes, the last being fatal. In addition, in the year before the final event, he developed rapid cognitive decline with contrast-enhancing lesions on MRI and highly elevated neurofilament light protein levels in CSF.

### Methods

Data and imaging were obtained from patient medical records.

### Results

At the time, the SCLS-like episodes were interpreted as myositis secondary to viral infection. A thorough workup for other causes, including genetic testing, was negative. As for the rapid cognitive decline, despite an extensive workup for infectious and inflammatory causes, no definitive diagnosis was made. Whole genome sequencing however identified a *C9orf72* hexanucleotide expansion.

### Discussion

The *C9orf72* expansion is associated with frontotemporal dementia and amyotrophic lateral sclerosis but has also been shown to increase susceptibility to neuroinflammation. Recent findings also suggest *C9orf72* to exert functions in the immune system, in particular regulation of type I interferon responses, in turn shown to be associated with SCLS. This case suggests a possible link between SCLS, cerebral inflammation, dysregulated type I interferon signaling, and expansions in *C9orf72*.

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Systemic capillary leak syndrome (SCLS) is a rare condition first described in 1960, with fewer than 500 cases reported as of 2016.<sup>1</sup> In the acute form, rapid extravasation of plasma fluid due to endothelial barrier dysfunction leads to hypotension, hypoalbuminemia, and hemoconcentration. In addition, in most patients, there is monoclonal gammopathy of unknown significance (MGUS). The cause of SCLS is unknown, and no common genetic basis has been identified, but immune dysregulation/vascular dysfunction has been suggested and viral infection is often identified as a potential trigger.

Hexanucleotide repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*) gene is strongly associated with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).<sup>2</sup> The normal function of the *C9orf72* protein is poorly understood, but a role in autophagy and vesicular trafficking has been suggested.<sup>3,4</sup> In addition to the CNS, *C9orf72* is highly expressed in myeloid cells, where loss of function is associated with immune dysregulation in mice.<sup>5</sup> Human expansion carriers might be at a higher risk of neuroinflammation and multiple sclerosis (MS).<sup>6,11,12</sup> Loss of *C9orf72* function leads to impaired endosomal function and reduced degradation of effectors in the stimulator of interferon gene (STING) pathway, important for regulation of type I interferon (IFN-I) responses, in human myeloid cells.<sup>7</sup>

## Methods

Data and imaging were obtained from patient medical records. The regional ethics review board waived the need for formal ethics approval. Informed consent to disclose was obtained from next of kin.

## Data Availability

Patient data may be shared after obtaining the appropriate approval from an ethics review board as well as the next of kin.

## Results

### Patient Characteristics

The patient was a previously healthy man in his late thirties. The family history was negative for autoimmune or neurologic disease, but significant for various psychiatric conditions. Notably, schizophrenia was diagnosed in his father with the age at onset of 36 years and featured hallucinations, violent behavior, and admittance to forensic psychiatry. There was no typical FTD-like presentation, but cognitive testing results were not available. The father died of pneumonia at age 70.

### Clinical Course

During a holiday trip abroad in May 2018, the patient developed acute generalized muscular weakness, vertigo, and lower limb edema that remitted spontaneously over a few weeks. Similar symptoms reappeared in September 2018, and he presented at the hospital emergency department (ED) with hypotension and generalized edema. Laboratory results were significant for a very high hemoglobin concentration of 210 g/L (ref. 143–170 g/L), low albumin, as well as elevated myoglobin and creatine kinase (CK) (Table). An infectious workup was positive for fecal enterovirus. Myositis triggered by enteroviral infection was suspected, and he was initiated on high-dose pulsed corticosteroids with significant improvement.

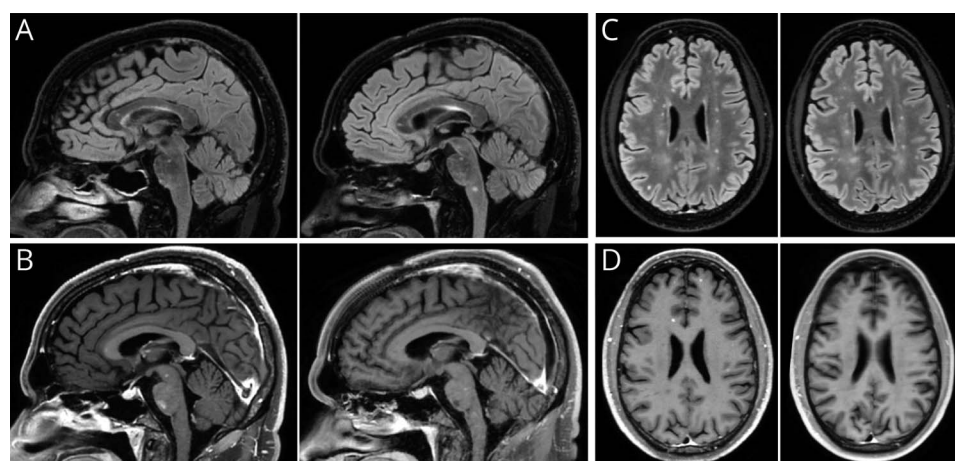
The third episode occurred in February 2019 when he presented at the ED with similar clinical and laboratory features as in the prior episode, however, now testing positive for influenza A. Again, he was started on corticosteroids. Unlike the previous episode, he worsened and was transferred to the intensive care unit for temporary hemodialysis. After discharge, he was referred to the hospital Centre for Hereditary Metabolic Diseases for further diagnostic workup. This included muscle biopsy with complete mitochondrial biochemical and morphological assessment as well as whole genome sequencing focusing on known genetic loci associated with recurrent rhabdomyolysis,

**Table** Findings at Presentation at the 3 Separate Episodes of Suspected Systemic Capillary Leak Syndrome

Findings at presentation									
Date	Body temperature	Blood pressure, mm Hg	Hb, g/L (ref. 143–170)	S-albumin, g/L (ref. 36–45)	Myoglobin, µg/L (ref. <59)	CK, µkat/L (ref. 0.6–3.5)	Echocardiogram	Infectious workup, positive findings	Tentative diagnosis at discharge
Sept 2018	Afebrile	Low (80 syst.), stabilized with resuscitation	210	24 at admission	2,770	154	Small amount of pericardial fluid	Enterovirus	Myositis/myopathy triggered by viral infection (enterovirus)
Feb 2019	Afebrile	Low (102 syst.), stabilized with resuscitation	208	No data at admission, 21.3 d later	655	16.5	Small amount of pericardial fluid	Influenza A	Myositis/myopathy triggered by viral infection (influenza A)
Jan 2022	38.8 C	Initially normal but dropped dramatically in a few hours	187	36 at admission, 21.6 h later	762	16	Small amount of pericardial fluid and poor ventricular motion	SARS-CoV-2	Idiosyncratic reaction to cyclophosphamide

Abbreviations: CK = creatine kinase; Hb = hemoglobin; Ref. = reference; Syst. = systolic.

**Figure 1** Representative MR Images of Brain Stem and Supratentorial Lesions During the First Months of the Inpatient Investigation for Cognitive Decline



Sagittal and axial sections from April 2021 are shown to the left and May 2021 to the right in each panel. Non-contrast FLAIR sequences are shown in A and C and contrast enhanced T1-weighted sequences in B and D. There were dynamic hyperintensities affecting the pons and scattered small foci in the supratentorial white matter and cortex.

mitochondrial disorders, and myopathies. There were no findings explaining the clinical presentation, but a small monoclonal component of 3–6 g/L (IgG lambda) was noted.

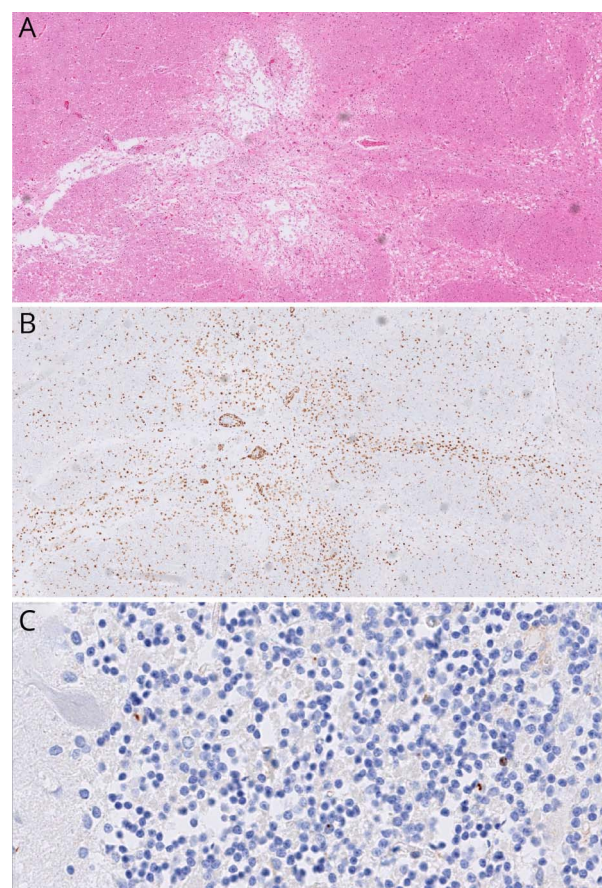
In March 2021, he was again admitted, but now for mental fatigue and lethargy since a few months and significant worsening in the prior weeks with apathy, slow movements, and impaired executive function. There was a Montreal Cognitive Assessment (MoCA) score below 20.

Repeated MRI scans showed dynamic hyperintensities on T2-weighted imaging with variable contrast enhancement, initially primarily affecting the pons, and including scattered small foci in the supratentorial white matter and cortex (Figure 1). A series of lumbar punctures showed highly elevated levels of neurofilament light protein in the CSF, but a notable absence of elevation in inflammatory markers (leucocytes, CXCL13, interleukin-6, and serum C-reactive protein) and albumin. The workup was negative for infectious etiologies, autoimmunity (including neuronal autoantibodies), immune dysfunction, vasculitis, prion disease, and malignancy. A broad genetic screen was performed, and an expansion in the *C9orf72* gene was identified, at the time not considered directly related. On the suspicion of atypical neuroinflammation/vasculitis, the patient was started on high-dose corticosteroids with some clinical improvement. He was discharged in the summer of 2021 with subsequent outpatient treatment with cyclophosphamide pulses.

The second pulse was administered in January 2022. Later the same day, he experienced lower back pain, fatigue, and confusion and presented at the ED somnolent and febrile with elevated hemoglobin, myoglobin, and CK. He rapidly deteriorated and became severely hypotensive, anuric, and stuporous, requiring intubation. An MRI scan showed widespread T2 hyperintensities along white matter tracts, and he tested positive for SARS-CoV-2. The next morning, he suffered a cardiac arrest and attempts to resuscitation were unsuccessful.

Autopsy revealed generalized tissue edema, and neuropathology showed multiple deliquesced lesions characterized by activated microglia/macrophages scattered throughout the

**Figure 2** Representative Images From Pathology



Bilaterally in the cerebral hemispheres and the pons (A, H&E, 5x), there were multifocal areas of disrupted white matter with activated microglia/macrophages (B, CD68, 5x). Several p62 immunopositive intranuclear and some intracytoplasmic inclusions were detected in the granular cell layer of the cerebellum (C, p62, 60x).



brain white matter (Figure 2). Some of these lesions appeared cavitating, probably reflecting varying age. While moderate amounts of inclusions immunoreactive for anti-poly-GP (C9orf72) and p62 (a marker of defective protein clearance) were visible in the cerebellum, there was no immunoreactivity for pTDP43, tau, amyloid beta, or alpha-synuclein.

## Discussion

We describe a previously healthy middle-aged man with several episodes suggestive of SCLS, a rare condition characterized by sudden vascular hyperpermeability. SCLS is commonly reported to be triggered viral infections, and genetic predisposition might contribute to an exaggerated response. In this context, it is notable that we found a hexanucleotide repeat expansion in the C9orf72 gene, which has been associated with dysregulated IFN-signaling through the STING pathway.<sup>5,7</sup> The clinical relevance of a dysregulated IFN pathway is further supported by the observation that C9orf72 expansion carriers are at higher risk of worsened outcomes with SARS-CoV-2 infection,<sup>8</sup> and a case report of fatal SCLS triggered by administration of interferon beta-1b.<sup>9</sup>

The patient also had an episode not typical of SCLS, with severe cognitive symptoms, substantial neuroaxonal degeneration, and focal blood-brain barrier (BBB) dysfunction. Neither during nor in between the preceding episodes of SCLS, there had been cognitive impairment. Of interest, traditional inflammatory markers were not elevated. Furthermore, although C9orf72 expansions are associated with FTD, pTDP43-positive inclusions were lacking with only a moderate amount of anti-poly-GP (C9orf72), exclusively seen in the cerebellum. This episode may be better explained by a dysregulated IFN-I response leading to BBB dysfunction. Indeed, the STING/IFN-I pathway has been shown to be crucial for brain leukocyte infiltration and BBB dysfunction in cerebral malaria,<sup>10</sup> representing a hallmark feature of this condition.

Partly similar imaging and neuropathologic features in context of SCLS has been reported previously but not involving genetic phenotyping.<sup>9,11</sup> SCLS is a rare condition, and previous genetic studies do not include sequencing with sensitivity to detect C9orf72 hexanucleotide expansions. However, an increasing body of evidence support a link between on the one hand STING/IFN-I and regulation of systemic and brain endothelial function and on the other hand C9orf72 expansions and STING/IFN-I. C9orf72 expansions have also been associated with an increased risk of MS.<sup>12,13</sup> Our case represents a documented clinical observation of an association of C9orf72 expansions with SCLS and BBB dysregulation, however, it does not provide direct evidence of a causative relation. To substantiate this notion, testing for C9orf72 expansions in a larger case series of SCLS and atypical cases of BBB dysfunction are required. Furthermore, studies involving animal models, cell lines, and pathology specimens will be needed to unravel underlying molecular mechanisms.

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