Inflammatory Markers of the Systemic Capillary Leak Syndrome (Clarkson Disease)

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Abstract

Objectives: The Systemic Capillary Leak Syndrome (SCLS) is a rare and potentially fatal disorder resembling systemic anaphylaxis that is characterized by transient episodes of hypotensive shock and peripheral edema. The pathogenesis of SCLS is unknown, and triggers for attacks are apparent only in a minority of patients. We introduce a clinical algorithm for the diagnosis of SCLS, and we investigated potential serum biomarkers of acute SCLS episodes.

Methods: We analyzed serum cytokines in a cohort of 35 patients with an established diagnosis of SCLS and characterized the effects of SCLS sera on endothelial cell function. We investigated the cellular source(s) of CXCL10, a chemokine that was significantly elevated in both basal and acute SCLS sera, by flow cytometry.

Results: Several cytokines were elevated in acute SCLS sera compared to baseline or sera from healthy controls, including CXCL10, CCL2, IL-1β, IL-6, IL-8, IL-12 and TNFα. The majority of acute sera failed to activate endothelial cells as assessed by surface adhesion marker expression. Monocytes appear to be the major source of serum CXCL10, and the percentage of CXLC10+ monocytes in response to IFNγ stimulation was increased in SCLS subjects compared to controls.

Conclusions: The presence of proinflammatory cytokines in acute SCLS sera suggests that inflammation or infection may have a role in triggering episodes. The enhanced capacity of monocytes from SCLS patients to produce CXCL10 suggests a new therapeutic avenue for SCLS.

Keywords: Systemic capillary leak syndrome; Inflammation; Cytokines; CXCL10; Monocytes

Abbreviations

SCLS: Systemic Capillary Leak Syndrome; HUVEC: Human Umbilical Vein Endothelial Cells; PBMC: Peripheral Blood Mononuclear Cells; ICAM-1: Intercellular Adhesion Molecule-1; VCAM-1: Vascular Cell Adhesion Molecule-1; IVIG: Intravenous Immunoglobulin; IFNγ: Interferon Gamma; TNFα: Tumor Necrosis Factor α; VEGF: Vascular Endothelial Growth Factors; Ang2: Angiopoietin 2; MGUS: Monoclonal Gammopathy of Unknown Significance

Introduction

The Systemic Capillary Leak Syndrome (SCLS) is a life-threatening disorder that occurs sporadically, typically in middle-aged Caucasians [1,2]. SCLS is characterized by recurrent, reversible episodes of distributive shock and anasarca due to sudden and unexplained leakage of plasma into the tissues. SCLS resembles, and is often erroneously diagnosed as, more common disorders such as sepsis, angioedema, and systemic anaphylaxis. Although a monoclonal gammopathy of unknown significance (MGUS) is highly associated with SCLS [3,4], its pathophysiologic significance is unclear. Therefore, because no specific biomarkers or pathognomonic clinical sign(s) of SCLS exist currently, the triad of transient hypotension, hemoconcentration, and serum hypoalbuminemia in the absence of underlying causes is sufficient to establish the diagnosis [2,5]. Fewer than 250 cases have been reported since Clarkson described SCLS in 1960 [2]. There is no specific treatment for acute SCLS other than hemodynamic support with intravenous fluids and vasopressors. Drugs such as theophylline, β2-adrenergic agonists, and most recently, imatinib, have been used as prophylactic agents to promote vascular integrity in SCLS [6]. Based on anecdotal evidence accumulated over several years, it has become apparent that monthly intravenous immunoglobulin (IVIG, 2 g/kg) infusions have severely curtailed attacks in a majority of patients who receive this therapy indefinitely [6-8].

Most research findings on SCLS have been based on single case reports, or purely clinical observations [2,6]. Using samples from our (then) 23-patient cohort, we reported previously that sera from SCLS patients during acute disease intervals uniformly induced hyperpermeability of human microvascular endothelial cell (HMVEC) monolayers due to disruption of endothelial adherens junctions and actin stress fiber formation [4]. In contrast, sera from these patients obtained during remission had little to no impact on HMVEC barrier...
integrity and resembled sera from healthy controls. HMVEC hyperpermeability elicited by acute SCLS sera was inhibited by pretreatment of target endothelial cells with IVIG or by antibody neutralization of Angiopoietin-2 (Ang2), a known mediator of vascular permeability that was elevated in acute SCLS sera compared to sera from healthy donors [4].

Although the trigger(s) of acute SCLS episodes are unclear, a longitudinal case registry study of 28 SCLS patients found that about three quarters of subjects experienced flu-like symptoms prior to attack onset [6]. Analysis of our expanded cohort (35 subjects) revealed elevated levels of several proinflammatory cytokines in acute sera, particularly CXCL10. Monocytes from a subset of these patients demonstrated an increased capacity for CXCL10 production. These results suggest a potential role for CXCL10 in the initiation of acute SCLS.

Materials and Methods

Study subjects

Patients were diagnosed with SCLS and classified according to established criteria described previously [2,6]. Patients were seen at the Clinical Center of the National Institutes of Health. Written informed consent was obtained from each patient, and the study protocol (09-I-0184) conformed to the ethical guidelines of the 2008 Declaration of Helsinki as reflected in a priori approval from the Institutional Review Board of the National Institute of Allergy and Infectious Diseases of NIH. Age-, sex-, and race-matched serum samples and lymphapheresis samples were obtained from the NIH Blood Bank.

Cells and reagents

Human umbilical vascular endothelial cells (HUVECs) were purchased from American Tissue Type Collection. Endothelial Growth Medium (EGM) 2 was obtained from Lonza. AlexaFluor 647-conjugated anti-ICAM1, phycoerythrin-conjugated anti-VCAM1, anti-CXCL10, phycoerythrin/Cy7-conjugated anti-CD14 antibodies and the protein transport inhibitor monensin were purchased from BioLegend. Phycoerythrin-Cy5-conjugated anti-E-selectin and APC-conjugated anti-CD19 antibodies were obtained from BD Biosciences. Qdot 605-conjugated anti-CD3 and Live/Dead fixable violet dead stain kit were from Life Technologies. Recombinant human TNFa and IFNy, and CXCL10 Quantikine ELISA kit were purchased from R & D Systems.

Cytokine measurements

Serum cytokines were measured using a Bio-plex Pro human cytokine 27-plex and a customized human cytokine 9-plex assay kit purchased from Bio-Rad according to the manufacturer’s instructions.

Endothelial activation marker analysis

HUVECs were seeded in 6-well plate and incubated overnight at 37°C. Cells were incubated with test serum (10% vol/vol final concentration) in growth medium for 4 hours. The cells were then detached with CellStripper (Mediatech), washed once with PBS, and stained with the indicated antibodies for 30 minutes. Cells were then washed twice, fixed with 4% paraformaldehyde for 10 minutes, and analyzed by flow cytometry.

CXCL10 measurement by ELISA

HUVECs were seeded in 96-well plate overnight at 37°C, and followed by incubation with test sera (10% vol/vol final concentration) in growth medium for 24 hours. Cell culture supernatants were collected and analyzed for CXCL10 by ELISA.

PBMC isolation

Peripheral blood mononuclear cells (PBMCs) were isolated from lymphapheresis samples using lymphocyte separation medium (LSM, LP BioMedicals). Briefly, apheresis samples were diluted 1:1 in PBS, and 30 ml of diluted sample was overlaid on onto LSM (15 ml) in a 50 ml conical tube. Samples were centrifuged at 800 x g in a table top centrifuge at room temperature for 40 minutes with break off.

Flow cytometric analysis of CXCL10 production

PBMCs were left untreated or stimulated with IFNy (20 ng/ml) in the presence of monensin overnight at 37°C. The following day cells were stained with Live/Dead violet staining kit according to manufacturer’s instructions and fixed in 4% paraformaldehyde. Fixed cells were permeabilized with blocking buffer (0.1% saponin, 1 mM CaCl2, 1 mM MgSO4, 0.1% BSA, 10 mM HEPES, 5% milk, and 5% human Fc receptor inhibitor, in PBS) for 30 minutes followed by staining with antibodies in blocking buffer for additional 30 min. Stained cells were washed twice and analyzed using LSRII flow cytometer (BD BioSciences).

Statistical analysis

Data were analyzed with the GraphPad Prism 6 software package. 1-way ANOVA or Kruskal-Wallis (for multiple groups) was used for grouped cytokine analyses, and unpaired parametric Student’s t test was used for flow analysis of CXCL10 production. P values < 0.05 were considered significant.

Results

Algorithm for the diagnosis of SCLS

SCLS should be considered in a patient with unexplained, transient hypotension and/or peripheral edema (Figure 1). If a temporally linked exposure (e.g. food, insect venom, drug) is suspected, elevated serum tryptase should exclude systemic anaphylaxis. Although our experience and that of others [6,9] suggest that acute triggers for SCLS attacks are often absent, viral-type upper respiratory and/or systemic symptoms may be present in many patients with SCLS prior to the onset of an episode. While catastrophic SCLS attacks are typically accompanied by massive edema of the face, trunk, and peripheral extremities, swelling resembling angioedema may be confined to certain areas (periorbital, back, and abdomen) in less severe episodes. Thus, complement factor 1 esterase inhibitor (C1 INH) levels and function should be evaluated in all patients with suspected SCLS to rule out hereditary or acquired angioedema.
Algorithm for diagnosis of SCLS

Episodic HYPOTENSION +/- edema

- associated trigger

Excluded acquired angioedema (C1 INH levels, function)

HEMOCONCENTRATION present

Fluid, pressor responsive

Exclude sepsis

Acute, transient HYPOALBUMINEMIA

Classic acute SCLS

+ associated trigger

Excluded anaphylaxis (serum tryptase)

Fluid, pressor unresponsive

Persistent edema, hypoalbuminemia, visceral effusions

MGUS (not required)

(chronic SCLS)

Figure 1: Clinical considerations in the prospective diagnosis of SCLS. After exclusion of primary cardiovascular and/or allergic causes, a diagnosis of SCLS should be entertained in patients with unexplained, transient hypotension and/or peripheral edema. Systemic anaphylaxis and hereditary and/or acquired angioedema can be excluded by measurement of serum tryptase during the acute episode and quantitative and functional assays for the complement component 1 esterase inhibitor (C1 INH). Although presumptive treatment for sepsis is prudent in the undiagnosed SCLS patient during the first severe episode, the hypotension and hemoconcentration of SCLS are typically refractory to intravenous fluid resuscitation, which exacerbates peripheral edema. Hypoalbuminemia due to protein extravasation is a hallmark of classic acute SCLS whereas low serum albumin levels and edema that does not resolve between episodes should prompt the diagnosis of "chronic" SCLS. MGUS is not universally present in SCLS and is therefore not required for the diagnosis.

Characteristics of the SCLS study cohort

We evaluated 35 patients with a confirmed diagnosis of SCLS based on the criteria outlined above and exclusion of other primary causes of hypotension and/or edema (Table 1). The median age at the time of the SCLS diagnosis was 46 years (range 22 months to 66 years).
although the vast majority of patients experienced clinical symptoms attributable to SCLS for several years prior to receiving the actual diagnosis. All but one patient was Caucasian, and 43% were female. Our cohort included three children and three adult patients with chronic edema. Most subjects experienced at least two episodes of SCLS per year, but the range varied widely, from once in five years to weekly. Overall, 86% had MGUS, and 27/29 M-proteins were of the IgG isotype. M-proteins were not detected in any of the children, whereas they were present in 91% of adults with SCLS. While most patients were treated with theophylline and terbutaline following diagnosis, 79% (23/29) experienced breakthrough episodes while on this regimen. Currently, 63% are treated with monthly infusions of IVIG (2 g/kg), and the majority of these patients (20/22) have been essentially episode-free for periods of up to eight years. One patient, a seven-year old child, is receiving subcutaneous IG because of IVIG intolerance. Two somewhat atypical patients (Pt. 3 and Pt. 31) experienced recurrent episodes of idiopathic hypotension, hemoconcentration, and hypoalbuminemia consistent with the diagnosis of SCLS, yet presented with unique symptomatology and did not respond at all to standard SCLS therapy, including IVIG. These patients also had M-protein isotypes unusual for SCLS (IgA or IgM, respectively).

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age at Diagnosis*</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Attack Frequency</th>
<th>Current Treatment Regimen</th>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>C</td>
<td>Every 4-6 weeks</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>F</td>
<td>C</td>
<td>Weekly/monthly</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>C</td>
<td>Every weekend</td>
<td>Infliximab</td>
<td>IgA kappa</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>M</td>
<td>C</td>
<td>&gt; 2/yr</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>F</td>
<td>C</td>
<td>5-10 day intervals</td>
<td>N/A (deceased)</td>
<td>IgG lambda</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>M</td>
<td>C</td>
<td>3-4 year intervals</td>
<td>Theophylline</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>M</td>
<td>C</td>
<td>3-5 year intervals</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>M</td>
<td>C</td>
<td>Single episode</td>
<td>None</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>M</td>
<td>C</td>
<td>3-4/year</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>F</td>
<td>C</td>
<td>Chronic</td>
<td>T/T**</td>
<td>ND#</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>F</td>
<td>C</td>
<td>Infrequent</td>
<td>T/T</td>
<td>IgG lambda</td>
</tr>
<tr>
<td>12</td>
<td>48</td>
<td>M</td>
<td>C</td>
<td>weekly</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>F</td>
<td>C</td>
<td>&gt; 2x/yr</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>14</td>
<td>51</td>
<td>M</td>
<td>C</td>
<td>&gt; 2x/yr</td>
<td>IVIG</td>
<td>IgG</td>
</tr>
<tr>
<td>15</td>
<td>53</td>
<td>M</td>
<td>C</td>
<td>Weekly</td>
<td>IVIG</td>
<td>IgG lambda</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>F</td>
<td>C</td>
<td>Chronic</td>
<td>Theophylline</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>17</td>
<td>43</td>
<td>F</td>
<td>C</td>
<td>3-4 year interval</td>
<td>None</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>18</td>
<td>64</td>
<td>F</td>
<td>C</td>
<td>Chronic</td>
<td>Theophylline</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>M</td>
<td>AA</td>
<td>3-4 yr</td>
<td>IVIG</td>
<td>IgG lambda</td>
</tr>
<tr>
<td>20</td>
<td>43</td>
<td>M</td>
<td>C</td>
<td>Bimonthly</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>21</td>
<td>65</td>
<td>M</td>
<td>C</td>
<td>Single episode</td>
<td>Theophylline</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>22</td>
<td>43</td>
<td>M</td>
<td>C</td>
<td>&lt; 2x/yr</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>23</td>
<td>36</td>
<td>F</td>
<td>C</td>
<td>&lt; 2x/yr</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>24</td>
<td>66</td>
<td>M</td>
<td>C</td>
<td>&lt; 2x/yr</td>
<td>IVIG</td>
<td>IgG lambda</td>
</tr>
<tr>
<td>25</td>
<td>40</td>
<td>F</td>
<td>C</td>
<td>Single episode</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>26</td>
<td>62</td>
<td>M</td>
<td>C</td>
<td>&lt; 2x/yr</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
<tr>
<td>27</td>
<td>7</td>
<td>F</td>
<td>C</td>
<td>Chronic plus acute</td>
<td>Subcutaneous IG</td>
<td>ND#</td>
</tr>
<tr>
<td>28</td>
<td>48</td>
<td>M</td>
<td>C</td>
<td>&lt; 2x/yr</td>
<td>IVIG</td>
<td>IgG lambda</td>
</tr>
<tr>
<td>29</td>
<td>61</td>
<td>M</td>
<td>C</td>
<td>3-4 year intervals</td>
<td>IVIG</td>
<td>IgG kappa</td>
</tr>
</tbody>
</table>
Increased CXCL10-producing monocytes in SCLS subjects

CXCL10, which is induced by many proinflammatory factors such as IFNγ, is secreted by many cell types including monocytes, endothelial cells, and fibroblasts during inflammation or infections [16]. To determine the cellular source of CXCL10 in SCLS sera, we studied whether CXCL10 production by peripheral blood mononuclear cells differed in control subjects and those with SCLS. As expected, percentages of PBMCs producing CXCL10 constitutively were low (data not shown), but IFNγ elicited dramatic increases in the number of CXCL10⁺ cells (Figure 4A). Whereas percentages of CXCL10⁺ T and B lymphocytes were low, about 30% of monocytes from healthy control subjects produced CXCL10 following IFNγ stimulation. Greater than 90% of all CXCL10⁺ mononuclear cells and CXCL10⁺ monocytes in SCLS subjects compared to healthy controls (Figure 4C). Taking together, these results suggested that in classic SCLS, endotheliopathy is probably not the major source of CXCL10.

Table 1: Clinical profiles of SCLS subjects.

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Episodes</th>
<th>Therapy</th>
<th>Time to diagnosis</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>43</td>
<td>F</td>
<td>Chronic plus acute</td>
<td>IVIG</td>
</tr>
<tr>
<td>31</td>
<td>58</td>
<td>F</td>
<td>Chronic plus acute</td>
<td>None</td>
</tr>
<tr>
<td>32</td>
<td>33</td>
<td>M</td>
<td>Chronic plus acute</td>
<td>IVIG</td>
</tr>
<tr>
<td>33</td>
<td>37</td>
<td>F</td>
<td>Chronic plus acute</td>
<td>IVIG</td>
</tr>
<tr>
<td>34</td>
<td>22 mo.</td>
<td>F</td>
<td>Chronic plus acute</td>
<td>IVIG</td>
</tr>
<tr>
<td>35</td>
<td>8</td>
<td>C</td>
<td>Chronic plus acute</td>
<td>IVIG</td>
</tr>
</tbody>
</table>

*Note: Many patients experienced episodes consistent with SCLS prior to formal diagnosis; **: Theophylline plus terbutaline; #: Not detected
Figure 2: Cytokine profiles of SCLS sera. (A-H) Serum cytokines were measured using a Bio-Plex Pro human multiple cytokine assay kit: VEGF (A), CXCL10 (B), CCL2 (C), IL-12 (D), IL-1β (E), IL-6 (F), IL-8 (G) and TNFα (H) (*P < 0.05, ** P < 0.01, **** P < 0.00001 Kruskal-Wallis).

Figure 3: Endothelial surface activation marker expression induced by SCLS sera. HUVECs were incubated with 10% (vol/vol) test sera for 4 hours (A-B) or 24 hours (C) at 37°C. (A) Surface expression of E-selectin, VCAM-1 and ICAM-1 was evaluated by flow cytometry. The dotted lines represent adhesion molecule expression induced by TNFα (1.25 ng/ml). (B) Paired comparisons of E-selectin, VCAM-1 and ICAM-1 expression induced by basal and episodic sera from each individual subject. (C) CXCL10 in HUVEC culture supernatants was measured by ELISA.
Figure 4: Abnormal IFNγ-induced CXCL10 production by PBMCs in SCLS. PBMCs were incubated with IFNγ and analyzed for CXCL10 production by flow cytometry. (A) Percentages of CXCL10+ cells among T lymphocytes (CD3+), B lymphocytes (CD19+), and monocyte (CD14+) populations from a representative healthy subject. (B-C) Representative flow plots (B) and analysis of CXCL10+ PBMCs and monocytes from SCLS subjects (n = 12) and healthy subjects (n = 14), presented as the fold control of the lowest value from a healthy donor for each individual experiment, set as '1'. *P = 0.02, unpaired t test.
Discussion

Among an extensive group of proinflammatory cytokines studied, we found that elevations in CCL2, IL-1β, IL-6, IL-8, IL-12 and TNFα were associated with acute SCLS episodes, and CXCL10 levels were both constitutively and acutely increased in SCLS sera. CXCL10 appears to be derived principally from peripheral monocytes, and SCLS patients have significantly more circulating monocytes with the capacity to make CXCL10 than controls.

We demonstrated increased VEGF levels in acute SCLS sera, which corroborated our previous ELISA results in sera from nine SCLS subjects (also included in the current group) [4], indicating that VEGF is a potential mediator of endothelial barrier dysfunction in SCLS. Although symptoms associated with viral infections do not precede SCLS episodes in all cases, some patients report episodes triggered by infections. Accordingly, we found increased quantities of CCL2, IL-1β, IL-6, IL-8, IL-12 and CXCL10 in SCLS acute sera, suggesting that type 1 immune responses T(1)(e.g., chronic viral, bacterial, or protozoan infections), rather than T(12) allergic immunity, may contribute the SCLS phenotype in at least a fraction of patients. Of all cytokines studied, CXCL10 was prominently elevated in both basal and acute SCLS sera relative to controls. CXCL10 has been shown to inhibit endothelial cell proliferation and induce apoptosis [17], a mechanism previously implicated in the pathogenesis of SCLS [18,19]. However, we were unable to demonstrate endothelial apoptosis induced by acute SCLS sera in our previous study [4]. In the current work, acute SCLS sera failed to activate endothelial cell adhesion marker expression (with one exception), and none of the sera elicited CXCL10 production by endothelial cells, suggesting that endothelial cells may not be a major source of CXCL10 in SCLS. Although IFNγ is a strong inducer of CXCL10, many T(1) cytokines are able to increase CXCL10 production by monocytes and macrophages. Because IFNγ levels were similar in SCLS and control sera, other factors including VEGF, TNFα, IL-β and IFNγ may act synergistically to elicit CXCL10 production by monocytes/macrophages in SCLS [20-22]. IFNγ-independent CXCL10 production may also occur [23]. For example, a single polynucleotide polymorphism (SNP) in the Cxcl10 promoter (-135G>A) enhanced its transcriptional activity in tuberculosis [24]. Thus, mutations or polymorphisms in Cxcl10 could also account for aberrant CXCL10 production in SCLS.

Because elevated serum levels of CXCL10 have been observed in many diseases including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis [25], and HIV infection [16], it probably has no utility as a specific diagnostic marker for SCLS. However, it may be useful for diagnosis and/or prognosis when considered with previously identified permeability mediators VEGF and Ang2. CXCL10 is a potent chemoattractant for monocytes/macrophages and activated T cells and promotes leukocyte transmigration through endothelium into inflamed tissues. Further study of abnormal CXCL10 production and its cellular source(s) may provide insights into the initial permeability-inducing trigger in SCLS episodes as well as uncover new therapeutic strategies for this potentially fatal disorder.

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