

# Idiopathic Systemic Capillary Leak Syndrome, A Case Report of an Eleven Years Old Girl with Review of Literature

## Abstract

Idiopathic Systemic Capillary Leak Syndrome (ISCLS), also known as Clarkson disease, is a rare disorder characterized by episodes of severe hypotension, hypoalbuminemia and hemoconcentration. Approximately 200 adult cases have been previously described in the medical literature.

To our knowledge only ten pediatric cases have been previously reported in the medical literature. We present here the eleventh pediatric case, an eleven year old girl who first presented during menarche with severe hypotension during the leak phase in early adolescence. Management initially included supportive measures and cardiopulmonary resuscitation. Preventative measures we have instituted include therapeutic trials of theophylline, montelukast, immunoglobulin (IVIG), and oral birth control pills to create anovulatory cycles - which have proven to be clinically successful for  $\geq 5$  years since her initial presentation. We describe her initial clinical presentation and clinical course, as well as a review of the literature below.

**Keywords:** Systemic Capillary Leak Syndrome; Recurrent shock; Hemoconcentration; Capillary leak; Clarkson's disease

## Case Report

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**Abbreviations:** ISCLS: Idiopathic Systemic Capillary Leak Syndrome; VEGF: Vascular endothelial Growth Factor; cAMP: Cyclic Adenosyl Monophosphate; MGUS: Monoclonal Gammopathy of Undetermined Significance

## Case Report

We present the medical history of an eleven years old girl which experienced three distinct episodes of cardiovascular shock with a variety of clinical presentations.

Her first known episode of Idiopathic Systemic Capillary Leak Syndrome (ISCLS) transpired during the winter of her eleventh year, coinciding with a community epidemic of H1N1 influenza. The patient was hospitalized for tachycardia, hypotension, hypothermia, hemoconcentration and hypoalbuminemia. She needed significant amounts of IV fluids, albumin and vasopressors to recover from a critical episode of hemodynamic hypotensive shock. PCR for H1N1 was consistent with an acute influenza infection in addition to a positive bacterial blood culture - as such both infectious causes were thought to have contributed to her initial presentation. No complications were evident post-discharge from the PICU and hospital.

Two months later, the patient presented with a second episode which manifested as reversible sinus tachycardia of unknown etiology. Like her initial illness, this was also preceded by mild cough, low grade fever, abdominal pain, vomiting, diarrhea and menses in three episodes.

It was not until her third presentation, that the diagnosis of ISCLS was more obvious due to its more "classic" clinical presentation. At this time she complained of pain in her lower extremities. On examination she was found to be diaphoretic and pale with perioral cyanosis, cold extremities, hypothermia (35°C), tachycardia (HR177/min), with delayed capillary refill (>5sec). In the emergency room she was found to be in hypovolemic shock. At that time her work up was notable for a hemoglobin of 20.9 g/dL, hematocrit 61.7%, platelets 406.000/mm<sup>3</sup>, CRP neg, HCO<sub>3</sub>=15.2 mEq/L, urea 38 mg/dL, creatinine 0.84 mg/dL, liver function test normal, prothrombin time 85%, activated partial thromboplastin time 33 sec, retic count 2%, blood smear: giant platelets, no abnormal cells, urine analysis normal, small cardiac index 0.4 on chest X-ray.

During the "leak phase" (which typically includes: hypoalbuminemia, edema, thirst, fever, diffuse pain, dyspnea, loss of consciousness) which lasted for 3 days, she had a decreased level of consciousness with severe cardiopulmonary shock, once again requiring hemodynamic resuscitation with IV fluids, albumin and vasopressors. She was started on IV steroids (solumedrol 1mg/kg/day) as well as fresh frozen plasma and Vitamin K. Because of her critical state and poor vascular access a central venous catheter was inserted and empirical antibiotic therapy was also initiated. Cardiac evaluation demonstrated good contractility on echocardiography and sinus tachycardia on ECG. Further labs ordered during admission revealed TIBC 52 microg/dL, transferrin 37mg/dL, LDH 288 U/L progressively increasing to 500 then 1730, haptoglobin=1g/L, ferritin=721.4ng/mL, Hb

electrophoresis normal, Vitamin B12 normal, flow cytometry normal, protein immunofixation was consistent with an absence of monoclonal bands (thus ruling out multiple myeloma). Metabolic investigations included normal ammonia level, high lactate= 31mg/dL and pyruvate= 1.8mg/dL possibly due to lysis. Tandem mass spectroscopy was normal. The patient also had peripheral edema in the lower extremities due to rhabdomyolysis. CPK increased progressively from 294 on day 2 to 21105 U/L on day 5, CKMB=156U/L. We thought of myositis due to pancuronium however her CPK kept increasing despite stopping sedation. She was found to have had no myoglobinuria.

On the fourth day of this PICU admission, her blood pressure stabilized, we slowly decreased her IV fluids and began diuretics to avoid fluid overload, renal failure and pulmonary edema. She unfortunately experienced severe edema of her left leg with significant pain and a compartment syndrome necessitating a fasciotomy.

At this time additional testing was found to be notable for: IgE, IgA, IgM, IgG were normal during this episode and when clinically stable. Her C3 was normal (on admission it was 10mg/dl then it rose to 119mg/dL on day 10). C4 was 25mg/dL normal. CH50 and C1esterase were normal. Liver enzymes were elevated and thought due to hypoperfusion after the hypovolemic shock. They improved progressively. All bacterial cultures were negative so preemptive antibiotics were stopped. PCR for influenza/H1N1 was also negative, so no infectious disease trigger was evident at the time of her third acute presentation.

She was discharged on a prophylactic drug regimen including: aminophylline 100mg three times per day, montelukast 10mg per day, IVIG 2g/kg monthly and birth control pills to produce anovulatory cycles. At the time of her most recent outpatient follow up visit, five years after her presenting episodes, she is asymptomatic and had no additional episodes.

## Discussion

ICLS was first described by Clarkson in 1960 and is thus known as Clarkson disease or spontaneous periodic edema. New cases have since been reported worldwide including in Lebanon, Kuwait, and India probably due to a better knowledge of the disease. Although almost 200 adult cases have been reported only 10 pediatric cases have been reported, to our knowledge. Two major studies regrouped American cases (Mayo-clinic registry) [1] and European cases (European registry) [2]. There is no apparent gender predilection. It is a potentially fatal disorder (mortality 30 to 76%) [3], characterized by repetitive attacks of hypotension leading to hypovolemic shock, generalized edema, hypoalbuminemia, without hypoalbuminuria, and hemoconcentration (elevated hematocrit).

Of the pediatric dataset previously reported, Onal et al. [4] published the youngest case a 5-month-old with intractable diarrhea, Foeldvari et al. [5] 3-year-old with hypovolemic shock without a trigger, Karatzios et al. [6] 6-year-old girl with recurrent hypovolemic shock and edema, Sion-Sarid et al. [7] 8-year-old with neurologic involvement, two cases younger than 18-year-old cited in the study of Mayo Clinic experience [1]. J kerketta et al. [8] systemic capillary leak syndrome in a 6 year old girl. Tadashi

Iwasa et al. [9] 10 year old girl with life threatening idiopathic capillary leak. Perme et al. [10] two episodes of systemic capillary leak syndrome in an 8-year-old boy, following influenza A virus infection. The young lady we present here is the only pediatric case and the third described case in the medical literature with menses temporarily related to the attacks. She had recurrent hypovolemic shock, hypoalbuminemia, edema, and hemoconcentration.

Idiopathic Systemic Capillary Leak Syndrome (ISCLS) can be divided into a series of distinct phases:

- a) Prodromal Phase: characterized by fatigue, light-headedness, flulike illness;
- b) Hemoconcentration Phase: occurring one to two days later: presyncope, oliguria;
- c) Shock Phase: Occurring minutes to hours afterward;
- d) Leak Phase: Hypoalbuminemia, edema, thirst, fever, diffuse pain, dyspnea, loss of consciousness;
- e) Post Leak Phase: One to two days after the leak phase a post leak phase occurs with restoration of intravascular volume takes place and cardiopulmonary failure could be the outcome [1,2,11].

## Complications

Complications of ISCLS, or Clarkson syndrome include compartment syndrome (manifested as rhabdomyolysis due to increased compartment pressure and muscular necrosis and diagnosed by increase creatinine kinase) [12,13]; renal and cardiac failure, ischemic brain injury, and liver injury due to hypoperfusion [14]; pulmonary edema, pericardial and pleural effusion (due to increased capillary permeability and fluid overload during resuscitation) [1]; generalized tonic-clonic seizures (due to autonomic dysfunction and cerebellar edema) [7]; acute encephalopathy (due to hemoconcentration and shock rather than leak of the brain capillaries because they seem less susceptible to the disease) [15]. In our ISCLS pediatric case reported here there was a clear link between menses and the onset of the attacks. However in the Mayo clinic review only one case had menses related crises and in other reports attacks were triggered in the peripartum period [1]. In our patient there was a clear temporal correlation with menses.

## Pathophysiology

The pathophysiology of ISCLS is still unclear. The capillary leak could be due to either increased hydrostatic pressure pushing the fluid and proteins to the interstitial space (in case of heart failure and renal failure), or a decrease in oncotic pressure (nephrotic syndrome, protein losing enteropathy, liver disease), or increased capillary permeability (sepsis, anaphylaxis, infections). The hypotheses in two case reports of ISCLS suggest an *immune dysregulation* with increase in circulating CD25+ and CD25+ T cells but no evidence of immunoglobulin or complement deposits on immunofluorescence [3,16]. Electron microscopy shows evidence of *endothelial injury and apoptosis* rather than vasoconstriction as the etiology of leak in ICLS. This hypothesis may be also supported by the fact that reverse of symptoms is delayed. However there is an overlap in the signaling pathways related to contraction

and apoptosis thus ICLS might be caused by the combination of both. Vascular endothelial growth factor (VEGF) is elevated at baseline and increases progressively during attacks [11,17]. IL-2 may be implicated in the pathogenesis of ICLS since there is high IL-2 expression in perivascular blood mononuclear cells of symptomatic cases as well as new emerging cases of ICLS with the use of IL-2 recombinant [11,18]. Several inflammatory mediators have been studied: *TNF-alfa* was persistently increasing in some affected individuals thus anti-TNF-alfa was suggested as possible treatment; also complements like *C4* where *C4a* rich plasma decreased the cardiopulmonary bypass related capillary leak syndrome [3,19,20]. Monoclonal gammopathy of undetermined significance (MGUS) is seen in 80% of cases where paraprotein levels (serum IgG1 with kappa light chains) increase during attacks and decreasing with remission. Special attention was drawn to these cases to rule out multiple myeloma that could develop later on in life as seen in some patients [20].

### Diagnosis

The diagnosis of ISCLS is based on the triad of hemoconcentration, hypotension, and hypoalbuminemia in the absence of secondary causes of shock.

Differential diagnosis of ISCLS includes: Idiopathic anaphylaxis, overwhelming sepsis, dengue shock syndrome, hereditary angioedema due to C1 esterase deficiency, systemic mastocytosis, chemotherapy, lymphoma, sezary syndrome, carbon monoxide poisoning, adrenal disease, myeloma, polycythemia Vera, inferior vena cava syndrome, carcinoid tumor, protein-losing enteropathy, and nephrotic syndrome [21-23].

### Treatment

The mainstay treatment of acute phase of ISCLS is adequate fluid resuscitation, vasopressors, fresh frozen plasma, albumin, and diuretics. Anti-TNF- $\alpha$  was reported to be effective in the acute phase in three cases whereby it is believed to increase cAMP [3]. Epoprostenol, a prostacyclin analogue promotes vascular smooth muscle relaxation [24]. In the chronic phase theophylline and terbutaline inhibit phosphodiesterase as a result adenosyl monophosphate (cAMP) increases and endothelial cell permeability decreases [1,4,11, 19,23]. Also maintenance of therapeutic drug levels was found to be associated with favorable results [24]. In addition  $\beta_2$  agonists may reduce the frequency of attacks [2], intravenous immunoglobulin used in high dose can reverse the leak phase (a patient survived 11years and others 8years and 1.5 years after starting IVIG) [25], Gingko biloba extracts may help in prevention. Plasmapheresis has been shown to decrease circulating paraproteins and might have possible temporary efficacy [1,4,21,23]. 10% Pentastarch, a high molecular weight molecule, was used successfully in the acute phase of two cases and found to prevent cardiovascular collapse [26]. Melphan or prednisone tried in the setting of myeloma or leukemia [17] has also been reported. *C4a*-rich plasma was studied in pediatric patients undergoing cardiopulmonary bypass and it decreased capillary leak related to this surgery [19]. Additional medications have reportedly been tried but efficiency has not been shown, these include: statins, Dasatinib or Imatinib, Bevacizumab, steroids, autologous peripheral blood transplant, Rituximab, Anakinra, Bortezomib [17].

### Conclusion

ISCLS is a rare disease that should be kept in mind whenever there is hypotension associated with hemoconcentration and edema. The possible triggers in the case of our patient menses, especially after an asymptomatic period consistent with anovulatory cycles, as well as infectious disease triggers.

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