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Idiopathic systemic capillary leak syndrome in childhood: A Literature Review

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ABSTRACT

Systemic capillary leak syndrome (SCLS), is a rare condition characterized by a recurrent stereotypical triad: hypovolemic shock, generalized edema, paradoxical hemoconcentration and hypoalbuminemia. It is caused by massive fluid extravasation into the interstitial space. Mortality may result from hemodynamic failure in the acute phase or cardiac failure due to reflex circulatory overload in the sub-acute phase. To date, twenty-one pediatric cases were reported in the literature. Sex ratio (M/F) was 0.32 with a median age at disease onset of 5.7 years and at diagnosis of 6 years. The disease was recurrent in 81% of patients with a median of three attacks. Severe complications were possible involving central nervous system (n=2) or rhabdomyolysis, with a compartment syndrome needing fasciotomy (n=5). The median time to clinical recovery was five days. Although the clinical manifestations of pediatric and adult SCLS were similar; in the opposite of adult SCLS, none of the children showed evidence of monoclonal gammopathy and three pediatric cases had a family history of SCLS. Seventy five percent of the patients were treated with prophylactic treatment (mainly immunoglobulins, theophylline plus verapamil). Several inflammatory cytokines were suspected to be involved in the pathophysiology of SCLS, especially interleukin-17 and tumor necrosis factor -alpha.

Introduction

Systemic capillary leak syndrome (SCLS), also known as Clarkson's disease[1], is a rare and severe condition characterized by a recurrent stereotypical triad: hypovolemic shock, generalized edema, paradoxical hemoconcentration and hypoalbuminemia[2]. It is caused by massive fluid extravasation into the interstitial space. Mortality may result from hemodynamic failure in the acute phase or cardiac failure due to reflex circulatory overload in the sub-acute phase[3]. The physiopathology of this disease is still debated. Yet, studies clearly describe an inflammatory substratum[4,5], and we have recently shown that interleukin-17 might be involved[6]. Approximately 170 idiopathic systemic capillary leak syndromes have been reported in the literature[7]. Here we review all the 21 published cases of pediatric idiopathic SCLS.

Review of the literature

We conducted a literature search to identify case reports of pediatric (<18 years) idiopathic SCLS. Briefly, PubMed was searched from January 1960 to October 2016 using the following keywords: "idiopathic capillary leak syndrome", "Clarkson's disease", "pediatric

idiopathic capillary leak syndrome", "pediatric Clarkson's disease". Among the 178 eligible articles, we finally selected 21 cases for further analysis[6,8-22] after exclusion of the adult patients.

The sex ratio (M/F) of pediatric cases was 0.32 with a median age at disease onset of 5.7 years (range: 17 days-17 years) and a median age at diagnosis of 6.0 years (range: 17 days-23 years). Three cases had a family history of SCLS. Individual characteristics and disease courses are summarized in Table 1. Four patients had only one attack, whereas the others experienced several ones with a median of three attacks (Table 1). A possible viral infection was suspected as a triggering factor for 11 patients (Table 1). Prodromal symptoms occurred in 17 patients, including flu-like symptoms in nine patients and gastrointestinal symptoms in nine patients (Table 1). Sixteen patients presented with edema (periorbital, facial, limbs, or generalized ascites) and among 16 patients who experienced hypotension, ten presented with hypovolemic shock. In addition, five patients had heart failure and a further six developed pulmonary edema during the recovery phase (Table 1). Two patients suffered from neurological complications (cerebellar edema or seizure) (Table 1).

Rhabdomyolysis was found in eight patients (Table 1). Five of them presented with a compartment syndrome and fasciotomy was necessary in five patients (Table 1). The median time to clinical recovery was five days (range: 1-27 days). Three patients[6,14,19] had biopsies (muscular or cutaneous), both showing non-specific abnormalities. C1

	Reference	Sex	Age at onset	Age at diagnosis	Attacks (n)	Prodroma	Trigger	Complications	Biological features	SCLS family history	Time to recovery
1	**Luquel**[8]	M	17 y	23 y	3	No	Season	APE	NA	Sister	24 hours
2	**Foeldvari**[9]	F	3 y	9 y	5	AbP	URTI	No	NA[a]	No	2 d
3	**Karatzios**[10]	F	6 y	6.8 y	2	AbP	*Influenzae* (H3N2)	Cpt Sd	NA	No	24 hours
4	**Onal**[11]	F	3 w	5 m	3	Diarrhoea	Diarrhoea	No	ARI	No	27 d
5	**Dowden**[12]	M	6 y	6 y	1	Fever, Nausea, Vomiting	No	Cpt Sd	ARI, RM, IL-6/TNF	No	5 d
6	**Kapoor**[13]	NA	NA	4 y	NA	NA	NA	NA	NA	No	NA
7	**Kapoor**[13]	NA	17 d	17 d	NA	NA	NA	NA	NA	Mother	NA
8	**Sion-Sar-id**[14]	M	5 m	8 y	5	AbP, Vomiting	No	APE, Heart failure, PRES Sd	ARI, RM	8 family cases	7 d
9	**Gousseff**[15]	F	5.4 y	5.7 y	4	NA	NA	NA	NA	No	NA
10	**Piastra**[16]	F	6 y	6y	2	Fever	No	No	ARI, RM	No	7 d
11	**Milani**[17]	F	34 m	48 m	4	Fever, Cough	URTI	Cpt Sd	ARI, RM	No	NA
12	**Iwasa**[18]	F	10 y	10 y	2	AbP, diarrhea	No	Cpt Sd	ARI, RM,G-CSF/IL-6	No	3 d
13	**Perme**[19]	M	8y	9y	2	Coryzal symptoms, Cough, Fever	Influenzae A	Heart failure	ARI, RM	No	7d
14	**Hsu**[20]	M	8 y	8 y	1	Coryzal symptoms, Vomiting	Rhinovirus, Para-influenza 3	APE	NA[a]	No	4 d
15	**Hsu**[20]	F	22 m	22 m	3	Coryzal symptoms	Respiratory Syncitial Virus	APE	RM[a]	No	NA
16	**Hsu**[20]	F	6 y	10 y	2	Coryzal symptoms	Influenzae A	Cpt Sd	RM[a]	No	NA
17	**Hsu**[20]	F	3 y	6 y	3	Coryzal symptoms, Diarrhea	Streptococcus A	APE	NA[a]	No	NA
18	**Hsu**[20]	M	4 y	4 y	3	Coryzal symptoms, Vomiting, Diarrhea	Influenzae A	Heart failure	NA[a]	No	NA
19	**Kerketta**[21]	F	6 y	6 y	3	No	No	No	NA	No	8 d
20	**Simonin**[6]	F	11.5 y	11.5 y	1	Myalgia, Arthralgia, Fever	URTI	APE, Seizure	ARI, TNF/IL-17	No	5 d
21	**Moreira**[22]	F	5 y	5 y	1	Vomiting	No	APE	NA	No	NA

Abbreviations: y: years, m: months, w: weeks, d: days; AbP: Abdominal pain, APE: acute pulmonary edema, ARI: acute renal impairment, Cpt Sd: compartment syndrome, NA: not available, PRES syndrome: Posterior Reversible Encephalopathy syndrome, RM: Rhabdomyolysis, SCLS: Systemic Capillary Leak Syndrome, Sd: syndrome, URTI: Upper Respiratory Tract Infection. [a]4 of this 6 cases have an increase of TNF.

Table 1. Physical and biological features of the paediatric idiopathic SCLS cases.

esterase inhibitor was normal when analyzed, while the inflammatory marker tumor necrosis factor (TNF)-alpha was high in six cases[6,12,20], and interleukin-17 in one case[6]. Surprisingly, none of the 15 children whose data were available showed evidence of the monoclonal gammopathy that is otherwise frequently seen in adult SCLS.

Therapy during the acute phase included massive intravenous fluid administration in all cases. Fluid administration led to severe complications during the repletion phase: seven patients suffered acute pulmonary edema and three patients presented with heart failure (Table 1). Inotropic drugs and/or mechanical ventilation were necessary in ten cases, intravenous or subcutaneous immunoglobulins and/or systemic steroids in eight cases, and anti-TNF therapy in one case[12]. After the attack, 12 patients received one or more prophylactic treatments: Gingko biloba alone (n=1)[8] or associated with terbutaline (n=1)[11], theophylline with terbutaline (n=4)[9,12,18,21], montelukast (n=1)[13], verapamil and aminophylline (n=1)[17] and immunoglobulins (n=4)[20]. Two deaths were reported: one occurred 2.7 years after the first attack[15], one in a 17-day-old baby during his first attack[13]. No one of the patients who died was on prophylactic treatment.

Discussion

The clinical and laboratory features of pediatric disease are highly similar to adult cases[13,15], except for two important differences. Firstly, monoclonal gammopathy has not been reported in the pediatric setting, in striking contrast to the high incidence (89%[15] or 76%[13]) observed in adult patients. The contribution of gammopathy to disease pathogenesis remains debated[23]. Also, we have found no evidence that gammopathy has any correlation with SCLS in children. Secondly, the occasional family history of SCLS in pediatric cases has not been reported in adults[13,15], suggesting that an inherited predisposition confers a higher risk of earlier presentation.

Neurologic involvement has been reported in only three adults[24] and in two pediatric cases thus far. Sion-Sarid et al[14]. reported a case of SCLS with neurological complications. In their case, the clinical and the radiological findings were similar to those of reversible posterior leukoencephalopathy syndrome, an uncommon neurologic syndrome, after rapid onset of severe hypertension. In our case previously reported[6], hyponatremia present during the acute phase could be partly responsible for a degree of brain edema and seizures. However, the origin of the CNS-abnormality remains unknown in our case. In both cases, the neurologic deficits and the MRI brain lesions completely resolved.

Therapy during the acute phase consists in fluid administration to stabilize hemodynamic instability. However, this fluid replacement should not be excessive because some patients affected with SCLS die due to complications of massive fluid repletion (acute pulmonary edema and/or heart failure).

Elevated inflammatory cytokines have been reported in patient's sera[20]. Remission samples of our patient's leukocytes exhibited abnormal patterns of cytokine secretion as levels of Th17 pro-inflammatory factors in supernatants of cultured PBMC were elevated compared to healthy controls[6]. Strikingly, these differences were more marked following in vitro leukocyte stimulation, suggesting that intrinsic differences in cytokine responses to biological stimuli in vivo might contribute to disease pathogenesis.

Conclusion

SCLS remains a rare disease in children but with increasing number of cases recently reported. Due to the extremely low incidence of pediatric SCLS, recommendation for treatment and pathophysiology studies might be better undertaken within the framework of an international registry.

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