Protein Losing Enteropathy after Fontan Surgery – Clinical and Diagnostical Aspects

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Summary
Protein losing enteropathy (PLE) is the massive enteric loss of serum protein. PLE may appear in several diseases associated with intestinal mucous membrane damages with or without infection. PLE is mostly associated with total cavopulmonary connection (TCPC) or Fontan-type circulation in patients with a functionally univentricular heart. TCPC is performed at an age of about 2 years or older and has a high survival rate of >90%. Time of PLE onset after TCPC is variable, the exact etiology is still unclear. Increased central venous pressure due to the absence of a subpulmonary ventricle may be a main reason for PLE, affecting 2–15% of the patients with a survival rate of 40% at 5 years and 20% at 10 years. Also immunological reasons for PLE are suspected. Major clinical signs are edemas, ascites, pleural effusion, diarrhea, malnutrition, fatigue, weight loss, and reduced physical development. The most impaired laboratory signs are elevated fecal α1-antitrypsin and α1-antitrypsin clearance, hypoproteinemia (hypoalbuminemia, hypo-γ-globulinemia), lymphopenia (selective T helper cell loss) and secondary lymphangiectasia. Therapy considerations should have the aim to decrease central venous pressure to improve hemodynamics. Medical treatment consists of substitution of e.g. albumin, γ-globulin, glucocorticoid, heparin or calcium, but still >60% of the patients remain symptomatic.

Zusammenfassung
Protein losing enteropathy (PLE), a massive enteric loss of serum protein, is usually characterized by a combination of different symptoms which do not have to be present at the same time. PLE appears in several diseases, e.g. in autoimmune diseases such as systemic lupus erythematosus (SLE) or celiac disease, and is often associated with intestinal mucous membrane damages with or without infection.

The medical history, physical examination and some laboratory parameters (table 1) are also specific for diseases associated with Fontan surgery (total cavopulmonary connection, TCPC). PLE is rare complication in patients who underwent Fontan surgery which is used to palliate complex congenital heart defects with an univentricular physiology [1]. Depending on the study, 9 [2] to 15% [3] of the survivors exhibit a substantial enteric protein loss. Time span between operation and the occurrence of PLE varies significantly from months to years after surgery. The mortality of patients with a manifest PLE is 46–59% after 5 years and >80% after 10 years [3, 4]. Up to now, the etiology of PLE is unknown.

**Etiology / Risk Factors**

The mechanism of action of PLE is poorly understood. The current theory of post-Fontan PLE is that chronic venous congestion causes the lymphatics to decompress into low-pressure cavities such as the pleural cavity or abdomen. Loss of proteins and lymphocytes, and an inflammatory response lead to chronic malnutrition resulting in a global immune dysfunction [5].

Systematic investigations correlating the risk factors for PLE with clinical parameters suggest elevated systemic venous pressure as a major contributory factor, which is the inherent hemodynamic component of the Fontan circulation [3]. However, there is no strict hemodynamic difference between those patients who develop PLE and those who do not [3]. Several studies suggest at least a participation of the immune system in the pathogenesis of PLE [6–8].

Recent observations indicate that onset of PLE is the result of multiple insults. It has been suggested that viral or bacterial infection, mostly of the gastric tract, can serve as trigger of multiple insults. It has been suggested that the disturbance of the immune system already prior to Fontan palliation. This finding may indicate genetic abnormalities. Reduced heparan sulfate accumulation in enterocytes contributes to PLE in a congenital disorder of glycosylation [16]. Also mesenteric hypoperfusion due to the increased mesenteric vascular resistance could serve as a possible trigger for the PLE development [17]. The results of Chaloupceky et al. [18] support the hypothesis that the abnormalities in the balance of coagulation factors observed in patients after Fontan operation are related to the coagulation factor production in the liver. The passive lymph loss caused by high central venous pressure does not explain the selective loss of CD4+ lymphocytes. Thus, it was suggested that the disturbance of the immune system could affect the structural integrity and patency of the intestinal wall, thereby triggering PLE [19]. The most likely explanation is that genetic factors and Fontan-induced venous hypertension predispose for PLE which appears upon a series of sequential or simultaneous environmental insults.

**Clinical Description**

Clinical signs for PLE are edemas, ascites, pleural effusion, diarrhea, malnutrition, fatigue, and weight loss as well as reduced physical development in children. The laboratory parameters required for the differential diagnosis of PLE are summarized in table 1 [data from 7, 8, 12, 19, 20]. Based on these very heterogeneous laboratory findings, PLE after Fontan procedure must be differentiated from other diseases with hypoproteinemia, other primary intestinal mucous membrane damages or primary lymphangiectasia.
– congenital enzyme defects (e.g. trypsinogen or entero-kine-

nase deficiency), malabsorption, nutrition sensitivity or al-

lergic reactions (gluten, milk components).

– nephrotic syndrome (low serum concentrations of γ-globu-

lin coinciding with elevated α1-, α2- and β-globulin levels

are present in both PLE and nephrotic syndrome, but in

contrast to nephrotic syndrome patients PLE patients gen-

erally do not exhibit proteinuremia).

– acquired (e.g. AIDS) or congenital immunodeficiency be-

cause of decreased T helper (T4) cell counts (up to

<100/μl) and γ-globulin levels.

The diagnosis of PLE is unspecific, even if there is always an

elevated fecal concentration of α1-antitrypsin indicating a

highly elevated α1-antitrypsin clearance. Nevertheless, since

α1-antitrypsin is an acute-phase protein, its increased oc-

currence in the stool did not allow for an unequivocal doubtless

diagnosis of PLE, as this symptom is also associated with

other conditions such as enteritis of different origin. In con-

clusion, it must be emphasized that PLE occurs rarely and in

combination with other nonspecific symptoms.

The clinical signs become significant most often after the pa-

tient underwent Fontan palliation. PLE with other etiologies

such as SLE, pericarditis or after superior vena cava-right pul-

monary artery shunt (Glenn) is extremely rare. Many patients

suffer from infections from various harmless origins while de-

veloping PLE [7]. For this reason patients are rarely examined

by a cardiologist at the very beginning of PLE occurrence.

Often patients already had edemas caused by hypoproteine-

mia before they are admitted to a cardiac center.

PLE is often associated with intestinal lymphangiectasia [3, 4,

21]. Although not yet routinely used for diagnosis, the com-

position of the peripheral blood of patients with PLE shows a

pathognomonic change, i.e. highly selective lymphocyte loss

(T4 (CD4+) cell count < 100 cells/μl) [7, 19, 20]. This selective

cell loss which is not yet completely understood leads to a dra-

matic decrease of the T4/T8 cell ratio similar to that observed

in patients with HIV [22, 23]. But in contrast to HIV patients

opportunistic infections are rare in PLE patients [20]. The

lymphocyte loss leads to the prevalence of unique T lympho-

cyte subtypes (CD4– CD8–) in the blood circulation [6, 24].

This phenotype of T lymphocytes is known from the autoim-

mune lymphoproliferative syndrome (ALPS) [25]. It is note-

worthy, that already children with Fontan circulation, but

without PLE, have an altered immune phenotype [24] com-

pared to age-matched healthy children [26]. However, also the

immune phenotype of children with other congenital heart

diseases may differ from that of healthy age-related subjects

[27].

Therefore a key tool is immunodiagnostics using either flow

cytometry [28] or microscopic (or slide-based) cytometry [29].

Both technologies [30] yield quantitative data on the pheno-
types and functions of leukocytes and lymphocytes [23, 31, 32]

and are increasingly important tools in hemotherapy and

transfusion medicine [33, 34]. Furthermore, cytometry can be

used to determine the concentration of multiple soluble blood

compounds by multiplexed bead arrays using very small sam-

ples volumes [35-37].

Management including Treatment

The prognosis of patients suffering from PLE is poor. Since

the pathogenesis is not yet fully understood, there is a broad

range of treatments suggested, mostly in single case reports.

Therapy considerations should have the aim to decrease cen-

tral venous pressure to improve hemodynamics. Relief of po-
tential obstructions in the Fontan pathway, conversion of a
classical atrio pulmonary anastomosis with loss of kinetic
blood energy due to severe atrial dilatation to a total cavopul-

monary connection or creation of a fenestration between the

systemic venous and pulmonary venous atrium are possible

surgical options.

The current medication consists of the substitution of albumin

and/or γ-globulin [38] in combination with diuretics but has

often only a temporary effect. In few patients PLE resolves

without any obvious correlation to therapy. Case reports indi-
cate that treatment with steroids, heparin, somatostatin ana-

logues or high-dose spironolactone can lead to an improvement

[11, 12, 21, 39]. Thus, anti-inflammatory therapy can at least

temporarily reduce TNF-α levels, and substitution of heparin
can diminish the protein loss by stabilizing the cell membrane

of the intestinal mucosa [39, 40]. Cure of PLE in sarcoidosis by

calcium substitution or anti-TNF agents indicating allergic or

other immunological etiologies have been demonstrated. Fur-

thermore, special diets (high protein, low fat with medium-

chain triglycerides and essential fatty acids) are suggested.

None of these treatments seem to be successful for all pa-

tients, reflecting the multifactorial origin of PLE. Correspond-

ingly, a detailed European study showed that, in spite of surgi-
cal intervention or medication, still >60% of the patients re-

main symptomatic [3] and that the 10-year survival rate of pa-

tients suffering from PLE is only 10–20%. For some, but not

all, patients with PLE the ultimate option is a heart transplan-
tation [41].

Prospects

Intensive studies about the reasons of PLE are needed to de-
velop therapies in the future. In our opinion, the monitoring
of the changes of the immune phenotype could be used to pre-
dict the PLE risk [8]. The difficulties of analyzing the changes
in the immune phenotype could be overcome by using cyto-
metric blood analysis [33]. The use of multiple analytes for a
rapid analysis of a multitude of cells and for the recognition of
specific cell types [29, 42] in combination with mathematical
analysis [9, 28, 43] could help to assess the risk of patients and
to individualize the therapy [44, 45].
References


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