Volume 1 Issue 1
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ES Journal of Ophthalmology

The eyes are the mirror of not just the soul!

Mini Review

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Received: Feb 01, 2020; **Accepted:** Feb 24, 2020; **Published:** Feb 29, 2020

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Eyes are known as most rich in capillaries quite evident to inspection because of the relative transparency of the tissues to allow vision. Multiple methods are used to study retinal and choroidal blood flow, as tools to evaluate systemic diseases that affect the microvasculature [1]. It is then straightforward to think about eyes to have a window of not just the local status of the capillary bed, as usual, but possibly about the general status of the microvasculature. This especially applies to those rare diseases where almost nothing is known except that a sudden generalized disease of the whole vascular bed does periodically arise: if an inflammatory agent is present, as the authors of the present contribution do hypothesize, among possible other co-causing factors, it should be dispersed all over the blood. In vitro assays show that acute, so called episodic serum is able to excite symptoms on a vascular tissue of a different subject, confirming the blood as vehicle of at least one, perhaps the major or unique, (co-) factor [2]. We are thinking about the so called Paroxysmal Permeability Disorders (PPDs) of whom one of the major experts in the world was the late Marco Cicardi in Milano, formerly director of Internal Medicine at University of Milan, together with associates like the first author, also interested in Heart Rate Variability (HRV), a keystone in that very same department with the late Alberto Malliani, previous director, and pupils, with all of whom we also had a cooperation history ever since [3-6] on such pervasive topic, not indifferent also in what we are discussing today as we will see; and GianMarco Podda, Assistant Professor and caring bright physician having cared a dear colleague and friend of us unfortunately affected by one such rare diseases. We are talking about a clinically heterogeneous group of diseases characterized by sudden recurrent increase in endothelial permeability leading to edema. Vascular leakage can be localized, as in different forms of angioedema, or generalized as in Idiopathic Systemic Capillary Leak Syndrome (ISCLS) [7].

Thanks to increasing knowledge of the pathophysiology of some forms of primary angioedema and to availability of more and more therapeutic options, the mortality burden has decreased over the years. However, the mechanisms underlying the acute derangement of the microcirculation during acute phases of many PPDs, above all ISCLS, remains uncertain [8,9].

PPDs are caused by sudden opening of endothelial cells' junctions in response to vasoactive mediators. Crises of ISCLS, also known as Clarkson's disease [10], usually develop through subsequent distinct phases: 1) Prodromal phase , with flu-like symptoms, abdominal pain, nausea and dizziness; 2) Shock (leak) phase, with shift of fluids and also high molecular weight proteins from the intravascular into the extravascular compartment leading to edema, hypovolemic shock associated with severe hemoconcentration (hematocrit >60%) and hypoproteinemia (total protein count <4 g/100mL); several possible complications may occur, including acute renal failure, compartment syndrome and neuropathy, rhabdomyolysis, myocardial edema, pericardial–pleural–abdominal effusion, deep-vein thrombosis; 3) *Recovery phase, with* gradual improvement of vital parameters due to progressive return of fluids (and afterwards proteins) into the intravascular space. This is a crucial turning point since fluid overload can carry the risk of potentially lethal

consequences as acute pulmonary edema or respiratory distress syndrome, pericardial effusion, cardiac tamponade and cardiogenic shock [8-12].

Nearly 90% of the described patients present with an immunoglobulin G (IgG) k monoclonal component but whether it has a pathophysiological role or it is only an epiphenomenon still needs to be elucidated [13]. So far no reliable biomarkers have been identified to follow the course of an acute crisis and adjust management accordingly.

Some preliminary hints about an alteration of HRV indexes during the acute phase of ISCLS are emerging [14]. Forces governing the fluid flux through microvasculature in the body tissues act according to the Starling's law. Usually, the trans-capillary fluid flow towards the interstitium is only partially reabsorbed into the capillary lumen driven by the plasmatic oncotic pressure. The excess of fluid (and proteins) remaining in the interstitial compartment is drained as lymph into venous system.

When a PPD crisis occurs, the excess of fluids and protein in the interstitial compartment may temporarily overwhelm the drainage capacity.

The lymphatic system is responsible for the transport of proteins that would otherwise accumulate in the extravascular compartments, but its response to "protein overload" as during acute ISCLS attacks is unknown [15].

Together with colleagues and friends in both our Universities we designed a research project whose aim can be summarized as follows: 1) Getting new insights into the role of the lymphatic system and its likely dysfunction in patients with ISCLS through innovative math modeling: in this respect, even *in vivo* capillometry could be of interest in the eyes besides other not too invasively accessible sites;

2) Characterizing interstitial fluid composition with devices as microneedle patches through the subsequent phases of the disease. This may help finding biomarkers which can prove useful also in the clinical setting; 3) Applying advanced Bioelectrical Impedance Analysis Technology Scales to assess patients' body fluid composition (Body Weight, BMI, Body Fat%, Water %, Skeletal Muscle, Fat-free Body Weight, Muscle Mass, Bone Mass, Protein, Basal Metabolism, Subcutaneous Fat, Visceral Fat, and Body Age) not only during acute and post-acute phases but also when the patients experience prodromal signs thanks to home measurement with easy -to-use scales, keeping track of all fluctuations on an app on their phone (connected via Bluetooth). These data will be compared to an age/gender-matched control group; 4) Collecting blood samples during the different phases of the condition to assess parameters as venous and arterial Hct, total proteins and albumin, monoclonal component, permeability mediators (as Angpt2, VEGF, NO) and Syndecan-1.

Rare diseases are indeed often neglected because large randomized controlled trials are not feasible and patients are usually spread over wide areas, referring to a wide number of centers.

University of Milan Internal Medicine Unit is to be considered a national reference Center for PPDs currently following 12 patients affected by ISCLS (which is such a rare disease that no more than 300 cases have been described worldwide so far). Available therapeutic approaches in PPDs and above all in ISCLS are not curative and they are mainly aimed at achieving an improvement of disease-related symptoms and prevention of recurrences and complications. The overall target of our project is thus to get deeper insights into the mechanisms involved in the pathogenesis of PPDs, with specific focus on ISCLS. These heterogeneous clinical conditions may be life-threatening and, except for hereditary angioedema due to C1 inhibitor deficiency, do not have specific diagnostic tests and optimal treatments. Understanding the role of the lymphatic system in ISCLS will be fundamental to provide better diagnosis and treatments to these patients. Assessment of interstitial fluid composition can provide markers for diagnosis and targets for the development of specific therapies. Data collected will allow deriving predictors which can prove useful for clinicians to follow disease activity, tailor treatments to each single patient and modify them dynamically according to specific needs. Studies on vasoactive mediators will test the involvement of biochemical pathways which can become targets of new therapeutic approaches.

It is useful to underline that among circulating factors, in ISCLS a pivotal role seems to be played by angiopoietin 2 (Angpt2) , which is a negative regulator of Tie2, a tyrosine kinase receptor located predominantly on vascular endothelial cells, able to promote endothelial cell survival, adhesion and cell junction integrity, thereby stabilizing the vasculature[16,17].

Preliminary studies in diabetic retinal edema indicate that AKB-9778, a small-molecule antagonist of vascular

endothelial-protein tyrosine Phosphatase (VE-PTP), increases phosphorylation of Tie2 even in the presence of high Angpt2 levels, thus restoring Tie2-induced endothelial stability and decreasing vascular leak [18-20]. This is remarkable, since VEGF antagonists have already revolutionized the treatment of diseases complicated by choroidal and/or subretinal neovascularization, as neovascular age-related macular degeneration, proliferative diabetic retinopathy and diabetic macular edema [21].

Given the state of the art, the project aims to provide the tools to develop new pathophysiologic and diagnostic approaches for PPDs through multitask investigations. Data obtained in this project will thus hopefully provide conclusive evidence on the role of the lymphatic system, body fluid composition during the subsequent phases of acute attacks in primary PPDs and will likely identify novel prognostic factors and pharmacological targets to treat these life-threatening disorders. The scientific and technological impact of the project will derive from application of innovative approaches to the study of PPDs thanks to joining of skills from a multidisciplinary team: practically, statistical inference in a understandable canonic deductive form will be conjugated with priors derived by more traditional math modeling in order to compensate weakness of every approach and improve each of them.

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