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Short Communication

Neurovascular, Eye and Systemic Capillary Anatomy: Could Clarkson's Disease be Among Promising Prospective Testbeds to Even Better Understand Ourselves?

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Systemic Capillary Leakage Syndrome (SCLS) - also known as Clarkson's sydrome from the name of the clinician observing and reporting it first time few decades ago [1] - is a tricky quite rare syndrome [2-4]: few tens of subjects have been known worldwide, of which 13 have been treated here in Milano at Sacco University Hospital under the responsibility of the late Marco Cicardi, former professor and general director for Clinical Medicine, together with his Assistant Professors, mainly Maddalena Wu also studying correlations with Autonomous Nervous Systems through Hearth Rate Variablity analysis [5], and Gianmarco Podda on the patient bed.

Causes are still unknown, and obviously there is no economical pharma interest in studying and possibly healing such a rare disease, but there is interest in governmental agencies, like our one, to invest little tax- payer money in order to better understand such pathology, that could also be informative about underlying physiology, as usual. The main evident effect is that, apparently asynchronously within life, repeatedly, and suddenly, capillary bed starts leaking all over the body – as opposite to local inflammatory diseases – almost like a general menstruation not involving just endometrium nor even just females.

What is known is that the agent, if any, is not in capillaries, but in the serum: after the crisis, the surviving patient restarts almost normally, while him/her so called "acute" serum is able to produce in vitro (probably then also *in vivo*) the same effect on a healthy capillary tissue from somebody else.

Interestingly enough, a still unknown monoclonal line is often, but not always, present in acute serum spectrophotometry, whose composition usually differs from patient to patient in composition of light and heavy polymerized chains, with a possible gender segregation, whose possible observation by

meta-analyisis of literature [6] is to be confirmed by higher numbers.

Moreover, if we measures as in figure 1 (reprinted from [6]) the weight daily oscillation (one patient happened to be a dear collaborating colleague) one can see a daily up and down oscillation in heathy or treated males, and females in the first half of the menstrual cycle, while in the second half females do seem to exhibit a kind of five-days-period cycle of increasing and decreasing, consistent with both the length of blooding on one side (curiously just on the 3rd slow cycle: kind of tri-merization in space is common in nature, like for Tumor Necrosis Factor signalling for internalize target cells [7], this one could just be a kind of tri -merization in time, as if some signal needs to be repeated 3 times in order to be effective), and with a much magnified in amplitude similar period in ill persons. A straightforward hypothesis by Anna Lunghi (personal communication) - I would strongly support her-would thus be a kind of female sexual hormone possibly mutated and decorticated from its natural cap - inactivating it until target in healthy subjects - thus signaling all the vascular bed to "hyper-menstruate": holes among plaques become are so big to loose even albumin from the vascular bed in acute episodes).

While not being in the vascular capillary wall the agent, such wall is nevertheless sensitive to such agent. It would thus be worth to study it, maybe in very well studied districts, like eye, where interdependency among vascularization and innervation is even more significant than elsewhere in the body (thus justifying neuro-

anatomy frontiers), also taking into account a neglected but of paramount important district at least here, the lymphatic one, where viscosity may affect transport and osmosis in a nontraditional way with respect to vascular bed, in turn emptied when acute, thus becoming not so different from lymphatic.

Figure 1: Time course of daily weight for the untreated (im), and treated (tim) ill patient, together with 2 healty females mother (hf) and 20 years old daughter (yhf) sharing home since ever thus synchronizing menstrual cycle.

This position paper, grounded in an interdisciplinary study project [8-11] conjugating inference and deduction in order to understand, forecast and possibly control also such disease, is then intended in order to stimulate the neuroanatomy community to consider the possibility to complement our not just vascular research in the direction I was suggesting and even beyond: we will not become rich, but we could discover something tricky, even possibly useful to understand more about a couple of pervasive, not completely understood, either compartments like lymphatic one, or phenomena, like menstruation.

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