Kwashiorkor — New evidence in the puzzle of oedema formation

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Kwashiorkor, a type of severe malnutrition associated with oedema, has been known for centuries but its mechanism remains elusive.[1] The low level of plasma albumin and the associated decreased plasma oncotic pressure has been for years the main explanation of oedema of kwashiorkor: an excess fluid flow from the capillaries to the interstitium was assumed to result from an imbalance of Starling's forces.[2] This mechanism seems plausible, as a low level of plasma albumin is a hallmark of kwashiorkor[3] and the Starling's principle shows that plasma oncotic pressure, largely determined by plasma albumin, is amongst the factors influencing fluid flow from the capillaries towards the interstitium.[4] For years, however, the implication of other mechanisms has been postulated, as there is an imperfect match between albumin levels and the degree of oedema.[5] Arguably, albumin level is not the only determinant of the plasma oncotic pressure which itself is only one of many variables determining the balance of the Starling's forces and this may explain some of the mismatch between albumin and the degree of oedema. Another explanation could be that the drainage of fluid from the interstitium to the lymphatic system is impaired. It is now accepted that, as a rule, fluid does not flow back from the interstitium to the venous end of the capillaries as initially assumed by Starling,[6] giving a leading role to the lymphatic system in regulating the volume of interstitial fluid. This important role of the lymphatic system has been a blind spot in the discussion about the mechanisms of oedema formation in kwashiorkor. This is surprising, as it seems that lymphatic drainage has the capacity to increase by a factor of 10 to 50 in case of excess fluid accumulation in the interstitium, providing a strong protection against oedema formation.[7] It can be argued that a moderate increase of fluid flow from the capillaries to the interstitial fluid cannot lead to oedema without a simultaneous dysfunction of this protecting mechanism.

The paper by Gonzales et al. in recent issue of *eBioMedicine*[8] gives important clues on oedema formation. First, by comparing children with and without oedema and children with similar albumin levels but different degrees of oedema, it confirms that low plasma albumin levels are necessary for oedema formation but that it is not the only explanation. Second, it gives some evidence that lymphatic drainage may be impaired, by showing an association between markers of the lymphatic function and oedema. This is an important piece in the puzzle of oedema formation.

Lymphatic drainage is an active and energy-consuming process involving mechanical fluid pumping by lymphatic valves, and thus, unsurprisingly, it is affected in malnutrition. It is not clear why lymphatic drainage is specifically affected in kwashiorkor, but evidence that markers of lymphatic function may be associated with oedema provides a new important insight in oedema formation.

The Gonzales et *al.* paper also shows evidence of extracellular matrix degradation in kwashiorkor patients. This factor has been suggested to be a possible contributing factor in oedema formation: it has been postulated that the interstitium behaves like a chromatography column, which can collapse in two phases when the chemical structure of the extracellular matrix is altered.[9] The role of such a mechanism should be taken with caution, however. The physical structure of the interstitium makes it very resistant to compression but easily disrupted when its hydrostatic pressure increases: a free liquid phase appears, leading to oedema, even in absence of any change in the chemical structure of the interstitium, as soon as this pressure becomes positive.[7]

The treatment recommended for kwashiorkor by the World Health Organization is the same as for other forms of severe malnutrition.[10] The new evidence provided by the paper of Gonzales et *al.* should prompt investigations on factors leading to this alteration of the lymphatic function to develop new approach really adapted to treat this life-threatening condition.

Declaration of interests

The author declares no competing interests.

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