Calciphylaxis: Another Piece of the Puzzle

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Calciphylaxis or calcific uremic arteriolopathy is a devastating disease; it generally occurs with little warning and is associated with severe pain resulting in a marked reduction in quality of life for those patients who are unfortunate enough to develop it [1]. Evidence-based treatment options with proven effectivity and safety are absent, which in turn makes management of the condition particularly challenging. Moreover, calciphylaxis occurs in patients despite a high degree of medical surveillance, that is, chronic dialysis patients highlighting our poor understanding of the etiology and consequently rendering us unable to prevent it. Facing all these circumstances, any progress in our understanding of the disease, any novel information helping to elucidate the pathophysiology and to identify risk factors is highly welcome.

The pathophysiology of calciphylaxis is complex and there is certainly more than one causative agent. A multifactorial dance of factors and pathways is required to turn the steady state of controlled end-stage renal disease (ESRD) into a milieu predisposing and finally causing the development of calciphylaxis.

We need to acknowledge that despite advances in our understanding of calciphylaxis several relevant issues remain unanswered. Unfortunately, all research efforts are constrained by the rare occurrence of the disease. Nig-

wekar et al. [2] have tried to overcome this limitation by retrospectively identifying cases of calciphylaxis from a huge database and checked for availability of tissue samples [2]. Their present paper meaningfully contributes to our understanding of calciphylaxis and provides valuable additional insights into this rare disease.

It was already understood that vascular calcification in small dermal arterioles is a hallmark of the disease and as such, it is used within the definition of the entity (calcific uremic arteriolopathy). Vascular calcification per se (both large and small vessel disease) involves various pathophysiological pathways and hence, unsurprisingly, several mineralization or calcification pathways have been linked to the development of calciphylaxis. One example was the canonical Wnt-signaling pathway including the soluble inhibitor sclerostin [3]. More generally speaking, it is widely accepted that an important contributing factor to calciphylaxis development is a misdirected calcium-phosphate metabolism. Misdirected in this respect means that the natural way of mineralization (strong in bone, absent in the vasculature) is disturbed and pro-calcifying activities are present in the vascular wall. Nigwekar et al. [2] add further credence to this hypothesis by detecting a significant stimulation of bone morphogenetic protein (BMP) pathway in skin samples from calciphylaxis patients.

BMPs contribute to physiological mineralization processes but also to ectopic calcification processes. Based on their comprehensive tissue analyses, the researchers were able to detect a significant upregulation not only regarding BMP, but also regarding other pro-calcification players such as *runx-2*. These factors have been identified in other disease conditions characterized by high levels of vascular calcification, but it is noteworthy that tissue from “healthy” ESRD patients (without calciphylaxis) did not show the same level of stimulated pro-calcifying factors. These data therefore identify another pathway supporting the etiological importance of pathological ectopic mineralization in calciphylaxis. In addition, the authors documented that activation of the biochemical master switch (BMP-*runx2*) precedes overt physico-chemical tissue deposition of calcium.

These findings have 2 important implications for further clinical and experimental research:

1. The present data fuel the hypothesis that it is not uremia per se, but a “second hit” (or numerous second hits) are necessary to switch on a sequence of events, which finally results in overt calciphylaxis. Moreover, the development of calciphylaxis is unlikely to be a linear, slowly evolving disease as we may have expected to see a higher prevalence of BMP and *runx-2* indicating early dermal calcification in non-calciphylaxis affected ESRD patients.
2. These findings allow us to speculate on preventive or therapeutic interventions targeting “bone formation” and re-directing calcium deposition to the skeleton in-

stead of soft tissue. If indeed calciphylaxis is a result of the activation of a pro-calcifying master switch, then this pathophysiological step during the process of calciphylaxis development might be preventable or open for therapeutic intervention.

Several calcification-focused interventional options are being investigated in prospective trials in calciphylaxis patients (e.g., sodium thiosulfate [NCT03150420], vitamin K [NCT02278692], SNF 472 [NCT02790073]). Their rationale is convincingly supported by the present data provided by Nigwekar et al [2]. The success of these and future clinical trials will ultimately depend on the nephrology community’s ability to support orphan drug trials in rare conditions, particularly in conditions such as calciphylaxis where the onset is rapid and transfer of patients to a “study centre” is not practical.

Improved awareness of the condition and the ability to promptly engage and recruit patients into such trials will bring us one step closer to finding viable therapies not only for the treatment of the condition but ultimately to prevent occurrence. In the interim, national and international prospective calciphylaxis registry activities will simplify data collection and analysis. Moreover, such registry activities will support treating physicians by providing a network of engaged clinicians to improve care for affected patients.

Disclosure Statement

The authors have no conflicts of interest.

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