No common final pathogenetic pathway in haemolytic uraemic syndromes

C. Mark Taylor, Alexander J. Howie and Julie M. Williams

Department of Nephrology, The Birmingham Children’s Hospital and Department of Pathology, University of Birmingham, Birmingham, UK

There is a long standing and widely held view that the many sub-forms of the haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) share a common final pathogenetic pathway. This was expressed recently in a review article in this journal [1]. This is an assumption which deserves to be challenged. It appears to be based on the concept that the histological hallmark of these syndromes, thrombotic microangiopathy (TMA), is a single entity. There is growing evidence that it is not.

Symmers originally used the term TMA to describe thrombi occurring in an arteriolar distribution, particularly at the junction between arteriole and capillary, in the absence of vasculitis [2]. Later, Habib found such lesions in infants with HUS and subsequently described different patterns of TMA, expanding the term to cover all of them. One form, remaining close to Symmers’ description, consisted of lesions at the arteriole with or without extension into the glomerular capillaries. In a second type, thrombosis was confined to the glomerulus, with endothelial swelling and amorphous material in the subendothelial space. The third form affected larger arteries as well as arterioles, and glomeruli appeared ischaemic. Various correlations were made between the histological sub-types and the clinical features of patients, and an extensive and valuable summary of this work appeared in 1992 [3]. In brief, arterial lesions were more often associated with severe hypertension and adverse outcome, while glomerular thrombosis alone was more favourable, as long as there was no co-existing extensive renal cortical necrosis [4]. Others have reinforced this view.

While the histological sub-type of TMA could be related to prognosis, early studies were not in a position to match this to the clinical groups discernable today. For example, much of this work was performed before the mid-1980s, the time when the commonest single cause of HUS became recognized, i.e. infection by verocytotoxin (shiga-like toxin)-producing Escherichia coli (VTEC). This precluded histological definition in the numerically most important group. Furthermore, it was only at the beginning of that decade that a prodromal illness of diarrhoea was shown to have prognostic significance, allowing a broad interim classification into diarrhoea-associated (D+) and non-diarrhoeal forms [5]. In Europe and the Americas, there is a close association between D+HUS and VTEC infection in children. On the other hand, non-diarrhoeal HUS in adults or children is a heterogeneous collection of rare diseases. Only a minority of patients...
falling into this category can be defined further, for example into inherited disorders of complement regulation, or associated with specific drugs such as quinine. This continues to pose a problem in making clinico-pathological correlations. Rarity reduces single centre studies to case reports or small series collected over long periods, and meta-analysis based on these is difficult because descriptive terms used by different authors may lack precision. Multicentre collaboration is therefore needed to match histology to well-defined larger clinical groups.

In spite of these restrictions, different pathological appearances are emerging. In VTEC-induced HUS in children there are glomerular thromboses [6–8]. Arterial thromboses do occur but are uncommon and appear to be a proximal extension of the glomerular lesion (Figure 1). These features are not seen in familial HUS with complement factor H deficiency, in which glomeruli show mesangial increase and double basement membranes [9,10] (Figure 2). There is no evidence of development of double glomerular basement membranes either acutely or up to 5 years after an attack of VTEC-induced HUS [11]. Most adults with non-diarrhoeal HUS have loose mucoid intimal thickening in small arteries with fibrinoid necrosis of arterioles resembling the changes seen in systemic sclerosis and accelerated hypertension [12] (Figure 3). In TTP, the characteristic abnormality is thrombosis confined to an arteriole at the glomerular hilum, and glomerular thrombosis is uncommon [12] (Figure 4).

It seems most unlikely that these different patterns are part of a single process distanced only by severity or duration. Almost certainly they represent separate end-points, and thus separate processes. This being the case, the assumption of a common final pathway becomes untenable. Present evidence leads us to consider HUS as a collection of specific diseases. Each one needs to be understood in terms of its aetiology, pathogenesis, prognosis and response to therapy.

The last point acquires clinical importance. If there is no final common pathway there is unlikely to be a single cover-all treatment. Treatments need to be tested in clearly defined specific diseases or groups. For example, there is a consensus view that plasma exchange can reverse some forms of TTP and atypical, non-diarrhoeal HUS. However, in a recent literature review of HUS management [13], no effective, evidence-based primary treatment could be identified for D+ or VTEC-induced HUS. This included plasma therapy. Better understanding of disease mechanisms and therapeutic options for HUS and TTP is a realistic target, and laying to rest the myth that these conditions...
have interchangeable pathogenetic features should help to accelerate the process.

Fig. 4. Glomerulus in a biopsy specimen from an adult with TTP. There is a thrombus in an arteriole at the hilum. PAAg.

References