



Thrombotic Microangiopathy

EDITORIAL COMMENT

Thrombotic microangiopathy: expanding genetic, clinical and therapeutic spectra and the need for worldwide implementation of recent advances

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Abstract

In this issue of CKJ, four reports address different aspects of a rare condition, thrombotic microangiopathy, including atypical haemolytic uraemic syndrome. For rare diseases, a single case report may provide hypothesis-generating information that may lead to concept-changing research with the potential to influence patient care. The present reports and small series illustrate the following aspects of thrombotic microangiopathy: (i) the role of whole-exome sequencing and of repeating the family history assessment over time in reducing the number of chronic kidney disease patients with non-specific diagnosis (e.g. focal segmental glomerulosclerosis without any further indication as to aetiology or hypertension-attributed kidney disease) and the need for further studies on the potential for type IV collagen mutations to be associated with thrombotic microangiopathy, i.e. the potential for an expanding genetic spectrum; (ii) the expanding clinical spectrum from an acute catastrophic disease to a chronic, mild, stable condition with unknown long-term consequences and uncharted therapeutic approaches; (iii) the expanding therapeutic spectrum, with the successful use of eculizumab to treat thrombotic microangiopathy in the context of overlap autoimmune disease and (iv) the huge worldwide inequalities in the implementation of these and other advances. International collaboration is needed to address these issues and should encompass the wider use of already available registries for this rare disease and the worldwide implementation of current effective, yet expensive, therapies.

Key words: alport syndrome, complement, eculizumab, plasma exchange, plasmapheresis, scleroderma

Introduction

The clinical spectrum of thrombotic microangiopathies encompasses primary and secondary diseases that may be relapsing and life-threatening, such as atypical haemolytic uraemic syndrome (aHUS) and thrombotic thrombocytopenic purpura [1]. For aHUS, the introduction of anti-complement therapy with

eculizumab has revolutionized the field [2, 3]. This issue of CKJ contains several articles that illustrate the advances experienced in the field of the pathogenesis and therapy of thrombotic microangiopathies, the expanding genetic, clinical and therapeutic spectrum and the dramatically different views of the issue from different corners of the world [4–7] (Figure 1).

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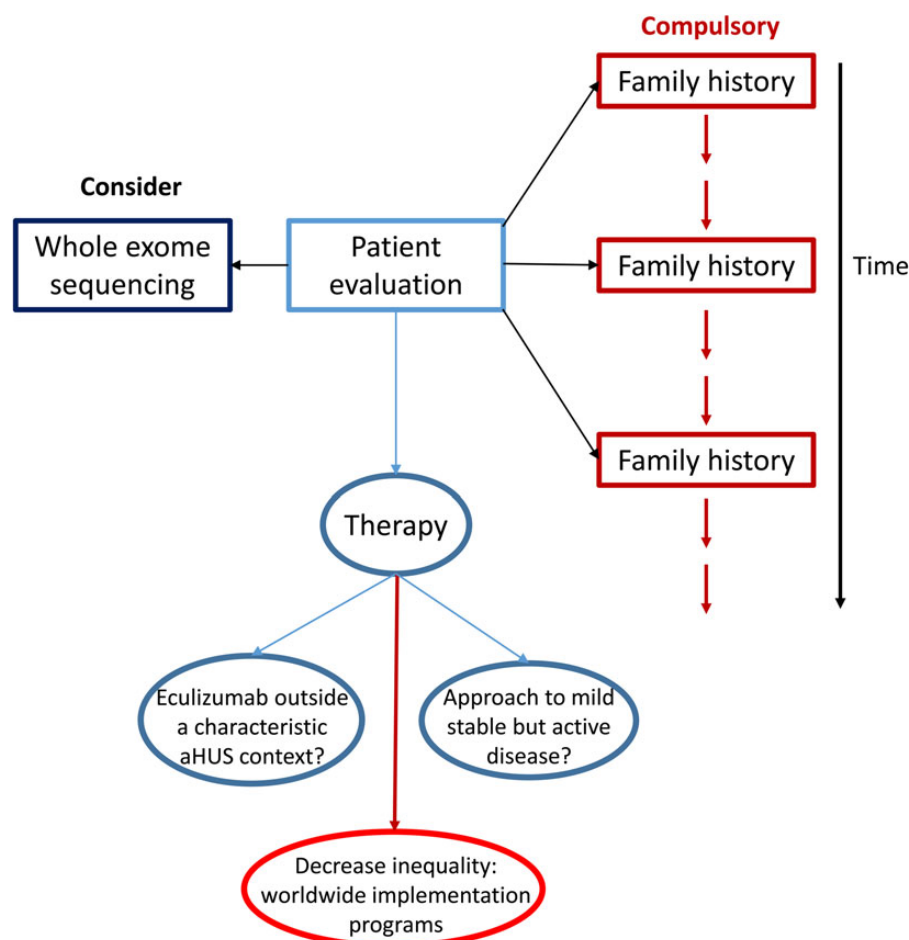


Fig. 1. Integrative view of lessons learned and challenges derived from CKJ reports on thrombotic microangiopathy.

The expanding genetic spectrum: COL4A5 mutations and the role of whole-exome sequencing in routine clinical care

Wuttke *et al.* [4] report an interesting case that is representative of the difficulties nephrologists currently have in assigning a cause of chronic kidney disease (CKD). A male teenager with evidence of chronic glomerular injury (high blood pressure, nephrotic syndrome and microscopic haematuria, progressing to decreased renal function) and mild intravascular haemolysis was sequentially diagnosed, based on renal biopsy, as IgA nephropathy, focal segmental glomerulosclerosis and membrane-proliferative glomerulonephritis with features of chronic thrombotic microangiopathy. A focussed genetic analysis in search of mutations associated with complement defects or proteinuric podocytopathies was negative. The patient received several therapies, some of them aggressive, such as immune suppression with cyclophosphamide and plasma exchange, based on the different diagnoses. The cause of kidney disease appeared to be finally settled by whole-exome sequencing. This case challenges conventional wisdom in several ways and is thus very enlightening for clinicians. First, it clearly shows the clinical potential of whole-exome sequencing, an approach that older clinicians might have dismissed, even if available, as a fishing expedition. Second, it illustrates the limitations of renal biopsy and questions traditionally held beliefs as to the major causes of end-stage renal disease. In the absence of biopsy or genetic analysis, the patient

might have been classified as focal segmental glomerulosclerosis, unknown origin or even hypertensive nephropathy, the most common non-specific diagnostic categories. Third, it illustrates the value of family screening and of the repeated assessment of family history since this may change over time as family members get older or new relatives are born and grow. While neither the patient nor his cousin had typical features of Alport syndrome and neither did a non-related family with the same mutation, mutation frequency analysis, the lack of other mutations and genetic analysis software and family history all predicted the mutation to be pathogenic.

Being a single case report, no firm conclusions can be drawn on the occurrence of thrombotic microangiopathy in patients with certain COL4A5 mutations, especially since haemolysis was not present in the cousin at the time of assessment and no information on features of thrombotic microangiopathy is available for the unrelated family in the literature with end-stage kidney disease sharing the same c.T665G mutation in the COL4A5 gene. Indeed, results for anti-complement H antibody testing were not reported. There are prior reports of aHUS in patients previously diagnosed with glomerulonephritis. In one series, three of six patients had glomerular nephropathies that had been associated with complement mutations that may potentially sensitize to aHUS, and indeed, all six patients had either mutations or risk haplotypes for such genes [8].

This report emphasizes the shift towards full genetic assessment that may characterize future nephrology practice [4] and

that has the potential to reduce the number of patients with end-stage kidney disease of uncertain origin or attributed to hypertension, as illustrated by the recent characterization of APOL1 variants as the underlying aetiology for hypertension-attributed CKD in African Americans [9, 10], or to focal segmental glomerulosclerosis, as exemplified by other cases of mutations in type IV collagen-encoding genes as emphasized by Wuttke *et al.* [4, 11].

The expanding clinical spectrum: stable chronic haemolysis following an episode of dialysis-dependent aHUS: is intervention needed and what is the long-term outcome?

Lopes *et al.* [5] describe a young woman who first presented with aHUS and acute kidney injury. The patient was found to have two genetic variants, one located in the CFH gene and one in the MCP gene, reported by the Polyphen-2 database to have a benign phenotype prediction. Following conventional treatment with plasma exchange, kidney disease parameters improved. However, microangiopathic haemolytic anaemia persisted for 4 years and the caretakers did not take further action to induce a complete remission. Within this follow-up, no progression of kidney disease was observed. This case raises several issues. First, it expands the clinical phenotype and suggests that some patients may present with just haemolytic anaemia for years that may go unnoticed, and even when noticed it may not be associated with the correct diagnosis. Second, it raises the issue of long-term mild activation of the complement system and intravascular haemolysis, resulting in release of potentially nephrotoxic factors such as haemoglobin [12, 13]. At first glance, this seems to be undesirable. Indeed, only longer follow-up, over decades since the patient was 31 years old at presentation, will provide an answer. In this regard, these patients should be offered the possibility to participate in a rare disease registry. However, no mention of participation in such a registry is made in the article, although several are available (e.g. European examples [14, 15], the Spanish aHUS Registry [16] and the Alexion-run Registry [17]). On the other hand, such a chronic disease condition is expected to activate compensatory mechanisms that will both increase erythrocyte production and limit secondary tissue injury. A detailed molecular study of such mechanisms may yield important information that may be added to and collated with that derived from animal models.

The expanding therapeutic spectrum for eculizumab

Thomas *et al.* [6] report a middle-aged female with positive PM-Scl antibodies, overlap autoimmune syndrome, hypocomplementemia and a clinical presentation and renal biopsy consistent with acute thrombotic microangiopathy in the context of scleroderma renal crisis [6]. A rapid recovery was observed following the introduction of eculizumab, despite previous failure of corticosteroids, plasmapheresis and renin-angiotensin blockade. However, no complement mutations predisposing to aHUS were observed, although a genetic variant of unknown significance was found at the C3 gene.

Being a single case report, firm conclusions cannot be drawn. One possibility is that aHUS coexisted with autoimmune overlap syndrome. However, this case report does raise intriguing questions about the role of complement activation in different forms of thrombotic microangiopathy and illustrates the concept that acute thrombotic microangiopathy may respond to eculizumab

even in a clinical context not suggestive of aHUS. A piece of information strikingly absent in such an autoimmune background is whether anti-complement factor H antibodies were present or absent.

Translational research T3: implementation of medical advances throughout the globe

The article by Reddy *et al.* [7] summarized the paediatric plasmapheresis experience in a South India centre between 2009 and 2013. This report represents a clear example of the gaps resulting from roadblocks in translational research T3 [18]. For research to benefit the worldwide population, three sequential steps are needed: the flow from basic research to clinical development [translational research type 1 (T1), bench-to bedside and back], from clinical development to clinical practice (translational research T2) and finally, from clinical practice to widespread implementation at all levels of society throughout the globe (translational research T3) through a combination of healthcare policymaking, education and guideline development, access to diagnostic and therapeutic resources and implementation [18]. Eculizumab was first marketed in the European Union on 20 June 2007 for adults and children with paroxysmal nocturnal haemoglobinuria [19], and in September 2011, the indication for atypical uraemic syndrome was granted [20]. However, at the time of acceptance of the Reddy *et al.* article in the summer of 2015, there were still no data on its use in the Indian subcontinent; the authors cite a 'prohibitively expensive cost' as a key reason. The manufacturer of eculizumab should establish, if they are not already in place, compassionate programmes that allow access to the drug at a reasonable cost in those countries where it is currently unaffordable. The alternatives, lifelong dialysis or transplantation or even death, are still expensive and in some places unaffordable, causing much human suffering.

In Reddy *et al.*'s report, aHUS accounted for 12/16 (75%) cases of paediatric plasmapheresis in an almost 5-year period [7]. All patients also received dialysis and steroids, and some additional immunosuppression. A high rate of anti-complement factor H autoantibodies (50%) justified the use of immunosuppression. The authors are reasonably satisfied with the results and argue that some patients started therapy late because of delayed diagnosis at other centres. However, every effort should be made to improve overall results. Within a short few years follow-up, 3/12 (25%) died or remained dialysis dependent and 6 (50%) had persistent CKD or hypertension/anaemia. Three (25%) had relapses and only three had a complete recovery, although given the young age and short follow-up, the occurrence of additional relapses, end-stage renal disease or death from the disease later in life cannot be ruled out. Even when diagnosis is delayed, patients may benefit from eculizumab, which may allow them to stop dialysis up to 5 months following dialysis initiation (reviewed in Rodriguez-Osorio and Ortiz [21]). In this regard, international consensus recommendations for the management of aHUS in children were recently published [22].

The way forward

In conclusion, several case reports in the current issue of CKJ and a small series point to a widening of the clinical, genetic and therapeutic spectrum of thrombotic microangiopathy as well as room for improvement in the worldwide implementation of current state-of-the-art therapeutic approaches. Case reports only provide hypothesis-generating information that should guide future research. The clinical spectrum of aHUS includes chronic

stable haemolytic anaemia that can be presumed to be the only manifestation for many years in an unknown percentage of patients. The long-term prognostic implications and therapeutic approaches, as well as the prevalence of this presentation, are still to be defined. A specific genetic defect of the COL4A5 gene was associated with thrombotic microangiopathy in a single patient. Why this was observed and what are the screening or therapeutic implications should be further explored, but this case report points to the role of whole-exome screening in routine clinical practice. Finally, the success of eculizumab in thrombotic microangiopathy apparently not related to aHUS raises questions about the role of complement targeting therapies in thrombotic microangiopathies in diverse clinical contexts. The wider use of already available registries for this rare disease will help achieve this research goals. In this regard, international collaboration is also needed for implementation in the developing world of current effective yet expensive, therapies.

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Conflicts of interest statement

None declared.

(See related articles by Wuttke et al. A COL4A5 mutation with glomerular disease and signs of chronic thrombotic microangiopathy. *Clin Kidney J* (2015) 8: 690–694; by Lopes et al. New combined CFH/MCP mutations and a rare clinical course in atypical haemolytic uraemic syndrome. *Clin Kidney J* (2015) 8: 695–697; by Thomas et al. Eculizumab for rescue of thrombotic microangiopathy in PM-Scl antibody-positive autoimmune overlap syndrome. *Clin Kidney J* (2015) 8: 698–701 and by Reddy et al. Plasma exchange for paediatric kidney disease—indications and outcomes: a single-centre experience. *Clin Kidney J* (2015) 8: 702–707.)

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