Can a dysregulated mucosal immune system in IgA nephropathy be controlled by tonsillectomy?

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Introduction

Even though IgA nephropathy (IgAN) is by definition a diagnosis requiring renal biopsy tissue examination in immunohistology, a well-grounded suspicion is possible in the presence of macroscopic haematuria, detected coincidentally or immediately following an upper respiratory or gastrointestinal tract infection. Many years ago, it was suggested that this hallmark of IgAN supported the hypothesis that the mesangial deposits of polymeric IgA detected by immunohistology are due to a mucosal immune system response to environmental pathogens [1]. Mucosal (or innate) immunity acts through recognition of pathogen-associated molecular patterns by Toll-like receptors (TLRs) expressed on phagocytic cells favouring virus or bacteria removal. The activation of TLRs induces dendritic cell maturation and migration to lymph nodes, leading to activation of specific T-cells and antibody synthesis, thus promoting a link between innate and adaptive immunity played at the mucosal and systemic level [2].

However, the discrepancy between the high incidence of viral syndromes in the general population and low prevalence of IgAN suggests that abnormalities of the mucosal and/or systemic immune system are critical for the development of IgAN, with infections representing a triggering event. Repetitive exposure to various infectious agents has been proved to induce experimental IgAN in animals only after abrogation of the natural process of mucosal tolerance which favours host defence after protracted pathogen exposure [3]. According to the hypothesis concerning the role of defective mucosal tolerance, patients with IgAN should have impaired elimination of mucosal antigens leading to continuous antigenic challenge, which triggers the production of nephritogenic IgA. Polymeric IgA molecules deposited in the mesangium in IgAN are mostly of IgA1 subclass, and present with a defective glycosylation and a reduction of galactose and/or N-acetylgalactosamine residues [4]. Also, in normal subjects, poorly galactosylated IgA1 circulates in the bloodstream after immune response to mucosal antigens or mucosal vaccines. Increased presence of degalactosylated IgA1 in the circulation is presently considered due to the misdirection of mucosal IgA1-committed plasma cells (with increased activity due to unknown mechanisms) to secrete mucosal type IgA1 into the circulation [5]. There, poorly glycosylated IgA1 undergoes formation of macromolecules due to self-aggregation or the reaction with antigens or IgG antibodies directed towards these glycoforms.

To sum up, the dysregulation of innate immunity in IgAN is likely to result in failure of mucosal antigen elimination and/or altered IgA1 synthesis and secretion. There is no need to postulate the action of peculiar antigens, as common microbial or food antigens may play this role. A variety of pathogens have been used in experimental models of IgAN, including Staphylococcus aureus in Th2-prone mice [6], oral immunization with Haemophilus parainfluenzae and repetitive intranasal immunization with Sendai virus [3]. Besides pathogens, gliadin or other com-
mon alimentary components can reproduce IgAN in mice [7,8]. Experimental models of oral immunization induced in mice a selective increase in specific IgA-producing plasma cells in the lamina propria of intestinal as well as the bronchial mucosa [9]. More recently, a model of disrupted tolerance has been reproduced in transgenic animals carrying a dysregulation of lymphotxin-like inducible protein (LIGHT). LIGHT-transgenic mice develop T-cell-mediated intestinal inflammation and increased plgA production and clearance, developing IgA mesangial deposits and renal damage as well [10].

What is the possible aim of tonsillectomy in patients with IgAN? For a long time, tonsillectomy was considered in treating patients with IgAN, aimed at removing a relevant source of pathogens, which can multiply in tonsil crypts, and also in macrophages and B-cells in lymphoid tonsil follicles [11]. This specific antigen challenge was thought to be able to elicit a supernormal IgA synthesis, as tonsil lymphocytes from IgAN patients showed a higher production of dimeric and undergalactosylated IgA1 than control subjects. On the other hand, tonsillectomy could be considered in IgAN as an easy mean to reduce the gut-associated lymphoid tissue (GALT) mass, even though submucosal lymphoid tissue is also largely represented in the intestinal wall, particularly in the appendix [12].

Benefits from tonsillectomy in patients with IgAN, accumulated over the decades, have been largely less impressive than expected. Tonsillectomy in IgAN was reported to be associated with a lower frequency of acute episodes of gross haematuria; nevertheless, the benefit for long-term renal associations with a lower frequency of acute episodes of gross haematuria; nevertheless, the benefit for long-term renal damage [16]. According to the paper by Piccoli et al., this seems to hold true also for mild and early cases. In regard to these observations, the present conclusion is that the proven benefit for tonsillectomy in patients with IgAN seems limited to cases in which tonsil removal was associated with immunosuppressive therapy. Prednisone or regular immunosuppressive schedules used after renal transplantation might enlighten the likely small benefit provided by tonsillectomy as an old and mild immunosuppressive tool for mucosal immunity. In conclusion, from the data presently available, it seems unlikely that a dysregulated mucosal immune system in IgAN could be ruled by tonsillectomy alone.

Conflict of interest statement. None declared.

References

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Behavioural abnormalities in children with nephrotic syndrome—an underappreciated complication of a standard treatment?

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Abstract

Behaviour and psychosocial adjustment are impaired in children with steroid-sensitive idiopathic nephrotic syndrome (SSNS). Both illness-related variables and family climate play a role. Steroid treatment—both short- and long-term—is an important contributor among other determinants. The exact mechanisms by which steroids lead to behavioural alterations in humans is unclear. Optimizing