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Clinical Involvement of the Tonsillar Immune System in IgA Nephropathy

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The temporal association of tonsillitis and hematuria or proteinuria in IgA nephropathy suggests that there might be a link between the physiological properties of the secondary lymphoid organ that tonsils represent and the mesangial deposition of IgA characteristic of this nephropathy. A number of clinical and *ex-vivo* data support this hypothesis. One of the earliest was the demonstration of the dimeric nature of mesangial IgA, composed of IgA monomers linked by a J chain, yet lacking the polyIg receptor acquired by secretory IgA during transcytosis through epithelial cells. This molecular structure is that of IgA synthesized in human tonsils, the epithelium of which lacks polyIg receptor. Moreover, tonsils from patients with IgA nephropathy display an abnormal partition of IgG and IgA producing plasma cells associated with a significantly developed web of high endothelial venules. IgA nephropathy could thus be in part related to an alteration of IgA precursors homing in tonsils. Tonsillectomy thus would present the advantage of removing an abnormally functioning source of dimeric IgA. Performed early enough in the course of the renal disease, tonsillectomy could suffice to halt the development of the nephropathy and restore the kidneys to health. *Key words: dimeric IgA secretion, human tonsils, mesangial deposits.*

INTRODUCTION

IgA Nephropathy (IgAN), as defined in 1968 by Berger and Hinglais (1) is characterized by the deposition of IgA in glomerular mesangium. This mesangial anomaly progressively leads to glomerular sclerosis, ultimately resulting in kidney failure. Several reports from the literature suggest that IgA are transiently deposited in the kidney, in a more or less continuous fashion. This is supported by the fact that IgAN patients often display bouts of hematuria or proteinuria, suggesting remitting/relapsing mesangial alterations. Moreover, it has been reported that transplanted kidneys from donors with previously undetected IgAN could "heal", i.e. clear the IgA deposits. Conversely, IgAN frequently relapses after transplantation, at least through the appearance of IgA deposits in the transplant (2, 3). These data suggest that mesangial IgA in IgAN originate from an extra renal source.

IGA SOURCES IN THE BODY

IgA represent the second most abundant isotype of immunoglobulins in plasma, after IgG. They also are the predominant isotype in secretions. Plasmatic and secretory IgA differ in their molecular form. The former are monomers, mostly of IgA1 subclass, while secretory IgA are synthesized as dimers, linked by a J chain (4). Secretory IgA reach the lumen of mucosal spaces by crossing the lining of the epithelium through the active use of the epithelial PolyIg receptor (PigR) which is cleaved from the apical pole of epithelial cells and remains attached as protection to secretory IgA. IgA2 are also more common among secretory IgA.

Plasmatic IgA have been widely studied in IgAN patients. It is thus well established that such patients often have increased serum IgA levels (5), with increased high molecular weight IgA (6). These IgA are polyclonal and no restriction pattern can be seen in high resolution elecrophoresis, although the pI range of IgA from IgAN patients tends to be more restricted than in controls (7). This could be due to the glycosylation anomalies reported in IgAN by several groups (8, 9). More precisely, an abnormal partition of galactosyl residues on IgA carbohydrate side chains has been reported (10, 11) that could be related to a defect in the enzymatic system of galactosylation. However, no anomaly of the galactosyl synthase genes has been observed so far (12).

The various physiological IgA sources have also been studied in IgAN. Anomalies have been reported in the bone marrow (13, 14) and in tonsils (15–20) while normal data were obtained from the study of gut samples (21, 22). There are no available data from the lymph nodes or spleen.

The molecular form of IgA in the mesangium has also been a topic of interest for several groups. IgA1 were found to be nearly exclusive (13) while both IgA1 and IgA2 were observed by our group (23) and others (24, 25). Mesangial IgA in IgAN also were demonstrated to contain J chain yet lack PigR (23), a molecular structure compatible with that of mucosal IgA before transcytosis, which was one of the major conceptual breakthroughs initiating the mucosal hypothesis of IgA nephropathy.

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THE MUCOSAL HYPOTHESIS

According to the data reported above, a pathophysiological hypothesis of IgAN could be that dimeric IgA are abnormally produced in a lymphoid organ, reach the peripheral blood, and, because of their size (and possibly charge) fail to be properly filtered by the kidneys but rather accumulate in the mesangium.

The possibility that palatine tonsils (or perhaps the whole Waldeyer ring) could be that extra-renal source of IgA is supported by several observations and studies. Recurrent ENT infections are reported by more than 70% of IgAN patients, often since childhood. These patients also report what was dubbed "synpharyngitic microhematuria" by Clarkson et al. (26), i.e. bouts of micro- or even macro-hematuria within 48 h of the onset of tonsillitis. Close examination of palatine and pharyngeal tonsils often discloses an enlargement in IgAN patients, considered pathologic enough by many ENT surgeons to sustain tonsillectomy.

Physiologically, tonsils are important lymphoid organs of the mucosae-associated lymphoid tissue. They contain germinal centers and plasma cells but produce no PigR. The immunoglobulins they synthesize drain from tonsils via blood and lymph vessels, and thus probably constitute a good part of plasmatic Ig. As in the rest of the MALT, cell recirculation is a major phenomenon in human tonsils. This physiological idiosyncrasy of the MALT involves anatomical "inducer" sites, which are mostly represented by Peyers' patches and solitary nodules in the gut, and "effector" sites consisting of the diffuse lymphoid tissue lining all mucosae. Human tonsils could be an inductor site, but also behave as an effector site because of their richness in plasma cells. Lymphocyte recirculation implies that specific cells activated in inducer sites then leave these tissues, through lymphatic vessels, reach the peripheral blood, then relocalize in lymphoid tissues or mucosal areas containing high endothelial venules (HEV). This allows a dissemination of exquisitely adapted specific immunity to all mucosal territories.

In physiological circumstances, human tonsils contain about 60% of IgG secreting plasma cells and 40% of IgA secreting plasma cells. However, in IgAN, these proportions are reversed, with 60% or more of IgA producing plasma cells (15, 16, 18, 19). This anomaly is associated with a highly developed web of HEV in IgAN patients, significantly more important than in controls. These HEV express high levels of adhesion molecules involved in lymphocyte recirculation (27).

The "tonsillar hypothesis" of IgAN pathophysiology would thus involve an activation of the mucosal immune system by environmental antigens, followed by either a higher output of IgA producing precursors and/or an increased trapping of these cells by activated HEV in tonsils.

Indeed, the study of peripheral blood cells in IgAN (28) shows significantly lower levels of IgA-secreting cells detected in ELISA spot, which is consistent with increased trapping of these cells. Also in support of such anomalies is the demonstration of a modified expression of adhesion molecules on peripheral B-cells, with significantly higher percentages of CD62L+/CD31+ B-cells with a significantly higher density of these molecules on the cells' surface (29). These data are both in favour of an increased activation of the MALT by environmental antigens and a better trapping of these cells by HEV. Increased activation is also supported by the fact that tonsillar lymphocytes from IgAN patients spontaneously proliferate more than cells from controls, as demonstrated by the significantly higher proportions of cells in S and G2 phase when analysing the cell cycle of freshly eluted tonsillar cells.

It has been shown that IgA produced by tonsillar B lymphocytes from IgAN patients were able to bind to the mesangium of human kidney glomeruli (30). Germinal center B cells appear to contain more B-1 (CD5+) cells with reduced susceptibility to Fas-mediated apoptosis in IgA nephropathy tonsils (31). Regarding the antigenic specificity of the Ig response of B cells, a tendency towards respiratory environmental antigens has been observed by us (unpublished results). In Japan, it has been reported that *Haemophilus parainfluenzae* antigens were able to stimulate preferentially T and B cells from tonsils of IgAN patients (32).

TONSILLECTOMY IN IGAN

A logical conclusion of all the considerations depicted above would be that tonsillectomy, rather benign surgery, could benefit IgAN patients by removing the source of abnormal IgA.

Tonsillectomy has been proposed by several authors (33–35) but the demonstration of the efficacy of this procedure is suffering from the fact that it cannot easily comply to classical criteria of randomized double blind therapeutic evaluation. Recently, a methodologically-sound study was however published, supporting the interest of tonsillectomy in IgAN (36).

Indeed, our group still has regular news from the first patient in whom tonsillar IgA plasma cells predominance was seen by us in 1983: He had a definite diagnosis of IgAN confirmed by kidney biopsy immunofluorescence. Since his tonsillectomy, he has not had any episodes of proteinuria or

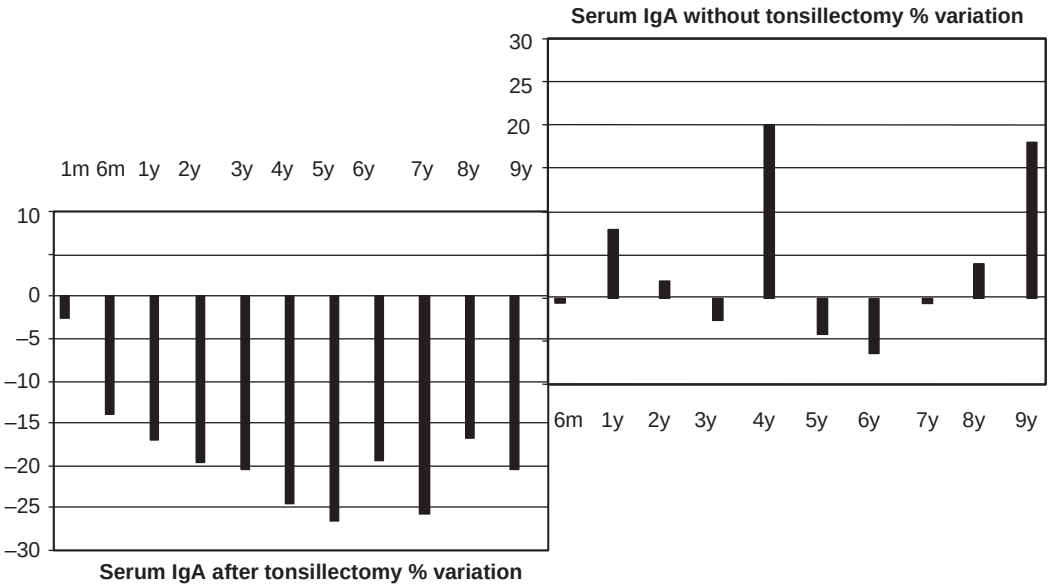

Fig. 1. Evolution over time of serum IgA levels in IgAN patients with or without tonsillectomy. Serum IgA were assayed repeatedly in 50 tonsillectomized IgAN patients and 21 patients who were not tonsillectomized. Follow-up was available for 9 years in both groups. A significant decrease in serum IgA was observed in tonsillectomized patients only, confirming tonsils as a possible source of abnormal IgA transiting towards kidney glomeruli via the peripheral blood.

hematuria and has not needed to see the nephrologist since.

In order to confirm this impression, we initiated a prospective series of IgAN patients follow-up (37). The cohort included 71 patients with identical renal parameters at inclusion, i.e. still mild glomerulonephritis. Among them, 50 were tonsillectomized and 21 were not. As shown in Fig. 1, plasmatic IgA levels rapidly and significantly decreased in tonsillectomized patients, while, overall, there was either no variation or an increase in non-tonsillectomized patients. Among tonsillectomized patients, 16 rapidly became lost to follow-up, usually because they did not feel the need to consult a nephrologist any more. For the 34 patients available for follow-up, the highly satisfactory evolution of creatininemia and proteinuria is shown in Fig. 2.

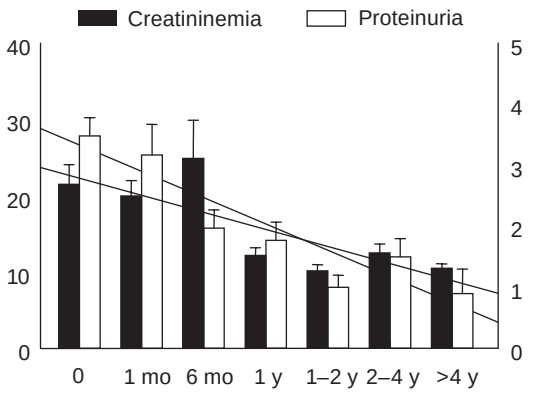

Fig. 2. Similarly, creatiniemia and proteinuria were measured after tonsillectomy in 32 IgAN patients available for over 4 years of follow-up and a steady and significant decrease was observed over time. This suggests that tonsillectomy, by decreasing the amount of abnormal IgA, allows for kidney healing.

CONCLUSION

A number of clinical and e*x-vivo* experimental indicators suggest that there is a rationale for considering therapeutic tonsillectomy in IgAN. However, it must be kept in mind that as tonsillectomy is merely removing the abnormal source of IgA, it will have no positive effect of the nephropathy if it is performed too late. Encouraging data has come from the recent Japanese studies. Tonsillectomy undertaken in children will, with time, prove most important as it might eventually demonstrate that IgAN incidence in this cohort was drastically reduced by this simple surgical procedure.

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