IgA nephropathy at two score and one

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On May 26–28, 2009, an international symposium on IgA nephropathy was convened in Stresa, Italy, as a Satellite Symposium of the World Congress of Nephrology held in Milan. This meeting was attended by a large number of scientists and clinicians working in the field of IgA nephropathy. The oral and poster presentations (over 70) ranged from very fundamental structural biology to clinical management. This article attempts to summarize the main findings of the meeting and to put forth some new perspectives and hypotheses regarding human IgA nephropathy on the 41st anniversary of its original description by Berger and Hinglais in 1968.

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The remarkable feature of the 12th International Gathering of the Acolytes and Apostles of IgA Nephropathy in Stresa, Italy, by the glimmering shores of Lago Maggiore (see Figure 1), was the coalescence of thought and discussion on a limited number of themes. Unlike prior meetings, one gained the distinct impression that science was honing in on such matters as defining pathogenesis, accurate prediction of outcomes, systematizing the approach to morphology of the disease, and enhancing diagnosis and treatment in a much more focused manner than heretofore in evidence. This is not to say that the topics discussed were not diverse, but they seemed to mostly play into a web of connectivity.

Not surprisingly, new data generated novel hypotheses, testable by future studies, and undoubtedly potential subjects for future meetings.

The comments that follow are not intended to be a comprehensive summary of the meeting but rather reflect the perspectives of a spectator (rather than a combatant) and of the two organizers in this dynamic arena of clinical and basic science, dealing with one of the most important and certainly most common of the primary glomerular diseases.

EPIDEMIOLOGY THEME

There is no doubt that IgA nephropathy is an extremely common 'disease.'[1] In reality, it is a clinicopathological phenotype, underlying which may be a remarkable degree of as-yet undiscovered heterogeneity of both etiology and pathogenesis. It seems quite clear that apparently 'normal' subjects (such as healthy living donors for kidney transplantation) do not uncommonly (4–16%; averaging about 70,000 per million population) have hidden or 'lanthanic' mesangial deposits of IgA (usually without co-deposition of IgG or C3).[2] It can be debated whether this is an 'innocent' finding or whether these subjects represent a state of 'pre-disease' awaiting another event (a second 'hit') to bring the disease to full clinical and recognizable expression. The ratio of subjects with 'lanthanic' glomerular deposits of IgA to those with clinically overt disease can be estimated at about 80 to 1; hence, conversion from a hypothetical 'pre-disease' to an overt disease by a postulated 'second hit' is quite an uncommon event. It is of interest that IgA nephropathy in the ddY mouse, which has considerable resemblance to the human disease, presents with a similar variability, including early and late-onset overt disease, and even covert disease

Figure 1 | Stresa, Lago Maggiore, Italy. Venue for the World Congress of Nephrology Satellite Symposium on IgA Nephropathy, May 2009.

detected only by renal biopsy.[3] As will be discussed below, we do not yet know whether these 'lanthanic' deposits share the biochemical characteristics found in overt IgA nephropathy, namely a predominance of IgA_1 isotype missing crucial galactose and sialic-acid-containing residues at some of the 5–9 glycan side chains in the hinge region.[4] If the 'lanthanic' deposits of IgA are the same as those found in 'disease,' then a re-assessment of the genetic association studies that used only overtly diseased subjects will be required. The alteration in galactosylation (and sialylation) of the glycans of IgA_1 would be predicted to alter the three-dimensional structure of the molecule (which normally is a highly planar T-shaped structure) and possibly affect its affinity and binding to intrinsic mesangial glycoproteins (such as fibronectin, laminin, collagens)[5] and plasma proteins (such as mannose-binding lectin and properdin)[6] just as it alters the binding to plant and animal lectins by exposure of normal cryptic ligands (such as GalNac) and by self-aggregation. Whether these biophysical phenomena relate to pathogenesis of the human disease will be discussed below.

GENETICS AND PATHOGENESIS THEME

It still remains unclear whether the aberrant glycosylation of IgA is transmitted in the germ line or whether it is acquired in sporadic IgA nephropathy, but similar defects in the main galactosyltransferase and sialyltransferase enzymes have been described in both familial and sporadic cases of IgA nephropathy, and elevated serum levels of galactose-deficient IgA are found in apparently healthy first-degree relatives of patients with overt IgA nephropathy but not in 'live-in' non-blood relatives (spouses).[7] Similar observations were confirmed during the satellite meeting in Stresa in Japanese and Chinese patients. These data strongly suggest a hereditable component to 'sporadic' IgA nephropathy, although at the same time they indicate the participation of additional factors, besides the presence of underglycosylated IgA1 in the circulation, to produce clinically overt renal disease. Conflicting data for *C1GALT1*, the gene encoding the key enzyme β1,3-galactosyltransferase, have been reported. Whereas in a Chinese population, IgA three single-nucleotide polymorphisms of *C1GALT1* have been reported in association with IgA nephropathy,[8] this was not confirmed in a French population reported by Berthoux in the meeting. In both Caucasian and Asian patients, no difference has been detected for *C1GALT1C1* encoding the β1,3-galactosyltransferase chaperone protein, Cosmc.[8,9]

The sporadic disease might be a consequence of a limited number of mutations in a single (or a few) common gene (s) or due to mutations in many genes, interacting with each other to produce the phenotype. This is a crucial issue that will require large-scale investigations including genome-wide association studies. Among the genetic factors possibly influencing the development of severity of IgA nephropathy, newly reported results indicated a possible role of transforming growth factor-β1 gene single-nucleotide polymorphisms or adhesion molecule (glycoprotein Ia or members of immunoglobulin superfamily) polymorphisms selected from multiple atherosclerotic disease-related genes. A genetic component in the regulation of production or expression of soluble myeloid IgA receptor (sCD89), which may relate to splicing mechanisms, has been also suggested.

The presence in circulation of aberrantly glycosylated IgA1 in patients with IgA nephropathy[10–12] was amply confirmed. Individual *O*-galactosylation patterns of serum IgA1 were reported by the Smith and Feehally group (Leicester, UK) to remain constant over long periods of time. These were also loosely associated with the severity of renal disease, but the overlap between different groups of progressors or non-progressors suggested that altered IgA1 *O*-glycosylation alone is insufficient to trigger progression. In agreement with this report, a collaborative study among Italian and US researchers, presented by the group of Camilla and Coppo (Torino, Italy), showed that the concomitant presence in patient sera of aberrantly glycosylated IgA1 and signs of oxidative stress, advanced oxidation protein products, and free thiol groups of serum albumin increase the predictive value for disease progression.

The elegant and ground-breaking studies of Suzuki, Novak, Mestecky and colleagues (Birmingham, AL, USA) using immortalized B cells from subjects with IgA nephropathy and normal controls[13] have shown that the aberrant galactosylation in patients is nonrandomly distributed among the glycan residues (only three specific sites are affected) and that premature sialylation of the GalNac residues, due to the heightened activity of α2,6-sialyl transferase, may interfere with galactosylation of GalNac. Cryptic epitopes related to GalNac, in a manner yet to be determined, lead to the production of autoantibodies to GalNac[14] that show a remarkable degree of restricted heterogeneity of the epitope binding sites. Taken together, these findings suggest that 'molecular mimicry' from environmental agents (such as ubiquitous bacterial and viral envelope proteins) may be involved in the autoantibody response to the cryptic, neo-antigenic GalNac sites on the aberrant IgA_1. They do not yet explain why IgG is not uniformly found, co-deposited with IgA, in the mesangial deposits of IgA nephropathy. Furthermore, no evidence of intramolecular or intermolecular epitope spreading of autoantibody reactivity, so common in many other chronic autoimmune diseases, has

yet been observed in IgA nephropathy, and a search for this phenomenon is warranted.

Nevertheless, IgA nephropathy has stigmata of a true autoimmune disease, in which both autoantigen and autoantibody are derived from the same general class of lymphoid cells (CD-19+ B cells) of mucosal (tonsils, gut) and bone marrow origin.[15] Integration of these seminal findings into a composite picture of pathogenesis of glomerular injury, however, remains incomplete. The dominant view, largely based on indirect observations, is that autoantigen (polymeric galactose deficient IgA_1) and autoantibody (oligoclonal IgG_1 and possibly IgA) join to form circulating immune complexes that subsequently deposit in the glomerular mesangium, perhaps by interaction with IgA receptors (such as the transferrin receptor, CD71) located on the surface of mesangial cells.[16] The group of Houda and Monteiro (Paris, France) reported that IgA from IgA nephropathy patients induces mesangial CD71 expression and cell activation in immunodeficient mice. CD89 may also have a pathogenetic role, as mice expressing human IgA1 and human CD89 develop IgA nephropathy.

The unique chemical composition and three-dimensional structure of the deposited immune complexes provoke a cascade of mediators (for example, mannose-binding lectin and properdin-dependent alternative complement pathway activation, cytokine and chemokines elaboration) leading to overt glomerular injury. Updates on the multiple biological effects of aberrantly glycosylated IgA related to pathogenesis and progression of IgA nephropathy were provided by Lai (Hong Kong) and Daha (Leiden, The Netherlands), focusing on complement activation[17] and glomerular-podocytic and glomerular-tubular cross-talk leading to the development of proteinuria.[18] Alternative pathogenetic mechanisms are also hypothetically possible; for example, the multimeric, aberrantly galactosylated IgA may acquire properties leading to its deposition in the mesangium (initially without antibody). These deposits could then serve as a 'planted' autochthonous antigen for subsequent interaction with autoantibodies from the circulation forming immune complexes *in situ*. In this scenario, the circulating immune complexes would be nonessential epiphenomena, and urinary immune complexes could be those 'shed' from the *in situ* deposits. In addition, the glomerular deposits of aberrantly galactosylated IgA (again in the absence of antibody) could locally activate mediators, such as mannose-binding lectin and properdin, directly because of their unique composition and structural configuration in tissue. Urinary C5b-9 was reported at the meeting as a possible prognostic factor in IgA nephropathy. A role for T-cell conditioning, including Th2 subset prevalence, Toll-like receptor activation on circulating lymphomonocytes, and altered T_{reg} and Th-17 subset regulation, was also reported. These postulated mechanisms or cofactors are not mutually exclusive, and additional studies will be required to confirm or deny their participation in the pathogenesis of human IgA nephropathy.

DIAGNOSIS AND PROGNOSIS THEME

Importantly, these fundamental advances in pathogenesis have opened up new avenues for the noninvasive diagnosis of IgA nephropathy (for example, anti-GalNac autoantibody testing, and quantification of serum under-galactosylated IgA_1) and will undoubtedly provide much new data bearing on the assessment of clinical activity of disease, its prognosis, and response to treatment, and perhaps shed new light on the well-known propensity of IgA nephropathy to recur in the transplanted kidney (see below). However, it is not likely that these advances will replace renal biopsy as the time-honored approach to evaluating patients suspected of having IgA nephropathy, at least over the short term.

The ability to predict the long-term outcome of IgA nephropathy has steadily improved over the past few decades and several new approaches were described at this meeting. Most notably, the first report of the ground-breaking Oxford classification of the pathology of IgA nephropathy[19,20] was presented and discussed. This international collaborative effort will be producing new data on the relationship of pathology to outcome for several years to come. It provides a new common language and a simple, user-friendly and reproducible systematic approach to categorizing glomerular and tubulo-interstitial lesions in IgA nephropathy having a likely bearing on progression. Although retrospective in design and requiring future prospective validation, the Oxford collaboration defined and scored four pathological parameters having an influence on outcome (independent of clinical information); including mesangial (M) and endocapillary (E) proliferation (hypercellularity), glomerulosclerosis (S), and tubular atrophy and interstitial fibrosis (T). These parameters were largely defined in adults and may have to be refined for children. The scheme will likely become known as the OXFORD-MEST scoring system. Necrotizing and crescentic lesions were not evaluated because of their rarity in the cases reviewed, and immunofluorescence and electron microscopy were not included in the enumerated parameters largely due to pragmatic considerations. It is not yet known whether these missing data points will prove to be a serious weakness in the classification schema. Future studies will be needed to confirm whether the OXFORD-MEST system represents an improvement over existing pathology grading systems, of which the most widely used has been that of Haas. The fact that the OXFORD-MEST system is based solely on light microscopy may be both an advantage and a disadvantage. It confers an advantage of applicability across a wide range of renal pathology centers, but it does not incorporate some of the newer pathological parameters shown to have independent prognostic import, such as phenotyping of the T-cells subsets[21] and enumerating the fibroblast-specific protein-1-positive cells in the interstitial infiltrate.[22] Transcriptomic analysis of microdissected glomeruli and tubules may also soon provide a new dimension of prognostication based on renal tissue examination, but proof of the utility of this approach will likely be slow to emerge. Time will tell if the new OXFORD-MEST system will

finally settle the long-standing and controversial issue of whether renal pathology makes an independent contribution, over and above simple clinical parameters, to the estimation of long-term prognosis in IgA nephropathy. This is a crucial issue having bearing on the design and execution of future controlled clinical trials of therapy, which depend on reasonably accurate appraisal of event rates (decline in glomerular filtration rate, doubling of serum creatinine or end-stage renal disease (ESRD)) in relatively homogeneous groups of patients in order to plan adequately powered but economically viable trials with clinically relevant end points. Perhaps future analysis of genome-wide association and single-nucleotide polymorphism studies may shed additional light on prognosis in IgA nephropathy, but such studies have not yet provided any useful data for individual prognostication. On the other hand, sophisticated studies of the biochemical composition of urine, including individual cytokines and growth factors and proteomic analysis,[23] are under evaluation in refining our current faulty prognostic capabilities in IgA nephropathy.

THERAPY AND TRANSPLANTATION THEME

Progress in treatment of IgA nephropathy has been slow (but relentless), largely because of the necessity for long-term observation to accrue sufficient primary end point events or to evaluate a biologically relevant change in renal function for statistical evaluation of cogent effects. Many studies have had to rely on surrogate end points, such as a decline in the magnitude of proteinuria. Nevertheless, a strong consensus has emerged that inhibition of the renin–angiotensin–aldosterone system (RAAS) is the desired *initial* approach to treatment of selected patients having features indicative of a poor long-term prognosis and a reasonably high risk of developing ESRD.[24,25] Controversy still exits as how to best achieve the goal of 'complete' inhibition of RAAS. Standard (regulatory authority approved) doses of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) fail to achieve a lowering of proteinuria in about 30–40% of patients. Supramaximal doses of *either* an ACEi *or* an ARB (often with salt restriction and/or diuretics) can in some circumstances show an enhanced effect on reducing proteinuria, but the long-term effects of this strategy on the development of ESRD are not yet fully understood. Dual therapy (using standard but maximal doses) of both an ACEi and an ARB (or an ACEi or ARB combined with a direct renin inhibitor or an aldosterone antagonist) may ultimately prove to be the treatment of choice but the limited trial data are not yet conclusive on this point.[26,27] Safety issues (hyperkalemia, renal artery stenosis) remain an unresolved concern. Slow escalation of ACEi or ARB monotherapy (with modest salt restriction and/or diuretics) dosing using *both* blood pressure control ($<125/80$ mm Hg) and a substantial decline in proteinuria (to <500 mg/dl is preferable than $>50\%$ reduction from baseline) as the goal of therapy seems to be the best current evidence-based approach. For those who fail to reach these goals, the addition of glucocorticoids (cyclical IV and oral) therapy (as in the Pozzi regimen) may provide additional protection from ESRD, but long-term failure is still seen (10-year renal survival of treated patients was 97%).[28] Perhaps the initial and simultaneous combination of *both* RAAS inhibition and steroid therapy will prove to be superior to either therapy given alone, but more trials are needed to show this conclusively. German multicenter studies (Eitner and Keller) are ongoing and their design was presented at the meeting.[29] The addition of cytotoxic immunosuppressive agents (cyclophosphamide and azathioprine sequential therapy, as reported by Ballardie and Roberts)[30] can be of benefit in progressive cases, and even more intensive regimens (IV methylprednisolone, cyclophosphamide, and plasma exchange) may be required for those uncommon patients with a rapidly progressive course associated with extensive crescents. Adjunctive use of fish oil therapy may be effective and is very safe when added to RAAS inhibition or to glucocorticoid therapy, but many patients fail to comply because of the disagreeable odiferous side effects. A number of proposed treatment regimens are either demonstrably ineffective or require much more investigation to be included as evidence-based therapy for IgA nephropathy. These include glucocorticoids combined with azathioprine: Pozzi reported no additional benefit obtained in a multicenter study, although Stangou in a single-center study found some greater effects in reducing the degree of proteinuria, and preserving renal function. The role of tonsillectomy in the management of IgA nephropathy[31] remains inconclusive because of the total lack of any randomized, prospective clinical trials with sufficiently long follow-up to assess the effects on progressive renal disease. Observational studies do support the beneficial effects of tonsillectomy on clinical features, such as hematuria and proteinuria, particularly in children and when used in combination with 'pulses' of IV methylprednisolone.[32] Some reports at the meeting focused on a possible benefit of adjunctive tonsillectomy to steroid pulse therapy on the clinical features of IgA nephropathy diagnosed as having a poor prognosis.

The optimistic side of the discussion indicates that we now have many options for treatment of IgA nephropathy that are evidence-based. It can be envisioned that these advances have somewhat reduced the overall risk for progression of IgA nephropathy to ESRD, but more needs to be accomplished in this arena. Hopefully, the astounding advances in the understanding of pathogenesis of IgA nephropathy will lead to more 'disease-directed' forms of treatment rather than the empiric regimens in use today.

Kidney transplantation is the ultimate 'treatment' for IgA nephropathy when all regimens fail to halt progressive disease. Unfortunately, even transplantation is not curative, as 30–50% or even more of the subjects so treated will develop a 'recurrence' of the disease in the allograft (or isograft) if followed for $\geqslant 5$ years.[33] But fortunately these recurrences have only a minor impact on overall graft and

patient survival, at least for the first decade after transplantation.[34] To be sure, some patients with recurrence do prematurely lose grafts from recurrence, but these are largely those with a very aggressive original disease (often associated with extensive crescentic glomerulonephritis or severe Henoch-Schönlein purpura).

Predicting the risk of recurrence is difficult and imprecise.[35] Several factors seems to be useful: (1) prior recurrence of disease and loss of graft from recurrence; (2) rapidly progressive course of the original disease accompanied by extensive crescents; (3) the use of zero-mismatched donors or living related donors. Two other postulated factors are controversial as they emanate from single-center studies and have not yet been independently confirmed; (4) the lack of treatment with an anti-lymphocyte or anti-thymocyte induction immunosuppressive regime regimen; and (5) the presence of IgA deposits in the transplanted kidney by 'zero-hour' transplant renal biopsies. In addition, the special risk of recurrence afforded by use of well-matched kidneys has not been uniformly observed and the long-term outcome of transplantation in IgA nephropathy is not different than other glomerular diseases after taking into account the donor source. Thus, the prospect of a recurrence should not dissuade clinicians from applying the benefits of renal transplantation to patients with IgA nephropathy and ESRD. With the possible exception of the use of anti-lymphocyte induction regimens, the post-transplant maintenance immunosuppressive treatment protocol has little or no effect on the risk of recurrence. The finding that the presence of 'lanthanic' IgA deposits in the 'normal' donor kidney (detected by 'zero-hour' renal biopsies) may have important relevance for pathogenesis of the recurrent disease. It should be presumed that circulating autoantibody to GalNac (see above) in some subjects with IgA nephropathy could react with the 'planted' and 'lanthanic' IgA deposits (if they are indeed deficient in galactose residues thus exposing the neo-GalNac epitopes) and promote recurrence. Whether this immunopathological recurrence would rise to the level of clinical detection would depend on the activation of accessory factors, such as complement and cytokines. This hypothetical sequence is not incompatible with a role for deposition of IgA containing immune complexes from the circulation as a causative factor in recurrent disease as well. This seems to be a rich minefield for future discovery.

CONCLUSION

In sum, like its predecessors, the Stresa gathering provided much new information to be digested and assimilated into the framework of IgA nephropathy. It also consolidated, confirmed, and codified an ever-expanding database of information about an enigmatic but extremely common disease. Combining the new with the old generates an increasingly complete picture of a disease phenotype and its underlying heterogeneity. New hypotheses, readily testable by current sophisticated methodology, were generated.

DISCLOSURE

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