IgA nephropathy

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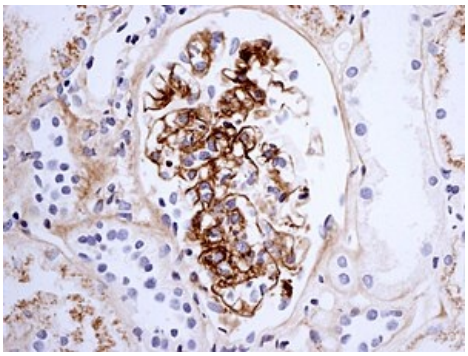
IgA nephropathy (IgAN) is the most common glomerulonephritis and cause of hematuria in the world. It is a chronic disease, however, with a relatively good prognosis compared to other glomerular diseases. Described in 1968 by Jean Berger, a Parisian pathologist, as a *nephropathy characterized by episodic hematuria associated with IgA deposition in the mesangium*.



IgA nephropathy in Henoch-Schönlein purpura

Etiopathogenesis

IgA

Immunoglobulin A is an antibody playing a vital role in **mucosal immunity**. It makes up 75% of all immunoglobulins produced in the body. IgA has two subtypes: IgA_1 and IgA_2, which differ in several ways. In the IgA_2 molecule, the heavy and light chains are not connected by disulfide bridges, as is the case with most immunoglobulins, but by non-covalent bonds. Furthermore, the gene for IgA_2 has a deletion in the coding region hinge region, which is therefore missing in the IgA_2 molecule. In contrast, the IgA_1 molecule contains a hinge region including amino acid chains that provide sites for galactosylation (as we will see below, galactosylation in the hinge region is an important etiopathogenetic factor in the development of IgA nephropathy).

IgA is divided according to the site of secretion into **mucous** and **serum**.

Mucosal IgA is the most common type of IgA. It is formed almost exclusively in the form of a polymer (pIgA) of IgA_1 or IgA_2. It contains the so-called *secretory component* (the rest of the transport Fc-receptor), which is bound to a dimer during secretion on mucous membranes. The main function of secretory IgA is **agglutination and neutralization of mucosal pathogens and toxins** and thus represents the first line of non-inflammatory defense of the organism.

Serum IgA is produced by plasma cells and then released into the blood. It is mainly monomeric IgA_1 ($mIgA_1$), and although it is the second most abundant immunoglobulin in the serum, its function is not fully understood. IgA_1 synthesized in the bone marrow have a relatively more galactosylated hinge region than mucosal IgA_1 and also have a high affinity to antigens. IgA is physiologically removed from the circulation in the liver. Clinical evidence is secondary IgAN arising in some cases of liver failure.

Pathological IgA

Patients with IgAN show **slightly elevated levels of IgA.** However, high IgA levels alone are not capable of eliciting the picture of IgAN. The pathogenesis of this disease is closely related to **galactosylation of IgA_1.** The properties of serum and mesangially deposited IgA_1 in IgAN are typical for mucosal IgA_1 (they are rather polymeric molecules with lower affinity to antigens). This led to the emergence of a theory that explains the origin of these IgA by the fact that a certain part of the IgA plasmablasts "missed" when homing back to the mucous membranes and ended up in systemic locations. This "mis-tracking" may be caused by the incorrect expression of surface "homing" receptors on the surface of lymphocytes or on the surface of the endothelium of mucosal vessels. Thus, the plasma cells find themselves in the bone marrow (and possibly also in the tonsils), from where they then form **mucosal IgA released into the systemic circulation and forming immunocomplexes** (IgA-IC).

The formation of immune complexes containing IgA is conditioned by several factors. **Secretion of $pIgA_1$** as a response to antigen is usually **prolonged**, as these antibodies have a lower affinity to antigens compared to mIgA. This lower affinity also leads to slower antigen clearance and consequent persistent production of IgA_1. The amount of circulating IgA increases and there is a tendency to develop IgA-IC. In addition, IgA molecules with altered galactosylation are thought to have a greater tendency to autoaggregate and form immunocomplexes with IgG directed against hinge region epitopes. Studies have also shown that these IgAs are **not capable of effectively binding complement**, which leads to the formation and persistence of IgA-IC in the circulation (complement stops the formation of immune complexes and participates in their internalization by phagocytes).

IgA-IC deposition and glomerular response

The deposition of IgA-IC is not necessarily an irreversible process, and the mesangium has the physiological ability to remove these immunocomplexes probably via their receptor-dependent endocytosis and subsequent catabolism, but only to a certain amount. In IgAN, mesangial accumulation of IgA-IC occurs because the rate of deposition is greater than the rate of removal, or because the deposits are resistant to removal for some reason. The deposition is a consequence of the increased concentration of IgA-IC, which results in non-specific capture in the mesangium. In addition, it is possible that it is also influenced by specific interactions between IgA and extracellular matrix components of the mesangium.

The extent and intensity of glomerular damage are extremely variable, and factors affecting immune complex deposition do not necessarily determine the extent of mesangial response. The development of damage after IgA-IC deposition is thought to be mainly due to IgA-induced mesangial cell (MC) activation and local complement activation. In response to the presence of the immune complex, MC activation, their proliferation and increased secretion of extracellular mass components and the growth factor TGF occur. In addition, activated MCs produce a number of different pro-inflammatory factors (PAF, IL-1, IL-6, TNF, etc.). IgA can also act on interactions between MCs and the extracellular mass and thereby induce mesangial remodeling. Activation of the complement cascade is not necessary for the development of IgAN, but is present in most cases (both local and systemic activation). IgA is able to activate complement through both the alternative and leucine pathways. The final product of activation, the terminal C5b-C9 complex, is capable of inducing MC activation and production of pro-inflammatory factors.

Morphology

The histological picture of IgAN is highly variable. It most often manifests as **mesangioproliferative glomerulonephritis** (GN), which shows expansion of the mesangium and endocapillary proliferation. Changes can be diffuse or focal. The second most common type of lesion is **focal proliferative GN**, where segmental proliferation is limited to a few glomeruli. Rarely, it may present with a picture of normal glomeruli or sickle-shaped GN. Leukocytes are not always present in glomeruli. Mesangial enlargement is the result of cell proliferation, extracellular matrix accumulation, antibody deposits, or a combination of the above. Immunofluorescently, IgA is found in all cases, sometimes in codominance with IgG in the glomerular mesangium. C3 and properdin also appear in most cases. When using electron microscope, electron-dense deposits in the mesangium are visible.

CITY Classification

The Oxford classification that identifies a patient's risk.

- Mesangial proliferation
- Endocapillary proliferation
- Segmental sclerosis
- Tubular atrophy / interstitial fibrosis

Epidemiology and Genetics

IgAN is more common in men with a peak incidence in the 2nd and 3rd decades. There are geographic differences in prevalence: from 30% in Asia and 20% in Southern Europe to very low prevalence in Northern Europe and North America. IgAN is mostly sporadic, but a genetic component and founder effect have been demonstrated in some latitudes, but no gene responsible for IgAN has yet been found.

Clinic

Clinical picture

IgA nephropathy most often presents in one of the following two ways: recurrent **macroscopic hematuria** (most often occurring immediately after upper respiratory or gastrointestinal tract infection) often associated **with proteinuria** or persistent **microscopic hematuria.** Rarely, patients may present clinically with acute renal failure and a rapidly progressing clinical picture.

Differential diagnosis

With its IgA deposits and possible involvement of the kidneys with hematuria, IgA nephropathy can resemble **Henoch-Schönlein purpura** (HSP). However, it is different in several ways: it has significant systemic symptoms (purpura, often joint and abdominal pain) and typically appears at a younger age (up to 20 years). IgA deposits are also found in other systemic diseases, e.g., chronic liver failure, Crohn's disease, gastrointestinal adenocarcinoma, ankylosing spondylitis, mycosis fungoides, Sjögren's syndrome etc.

Prognosis

In most patients, IgAN has a benign course. 5–30% of patients achieve complete remission, while others have persistent hematuria. Renal function is usually very well preserved in these patients. However, 25-30% have a progressive form, where stage 5 chronic renal insufficiency occurs within 20-25 years. This risk is variable in different populations. Indicators of unfavorable prognosis are hypertension, proteinuria, male gender, older age at disease onset, and extensive glomerulosclerosis or interstitial masses on renal biopsy. Proteinuria lasting more than 6 months has the highest predictive value for an adverse impact on kidney function.

Therapy

There is no optimal therapy for IgAN. ACE inhibitors are used in patients with proteinuria or reduced renal function. Tonsillectomy and fish oil have been suggested as possible benefits for patients with IgAN in some small studies. If there is a clinical picture of rapidly progressing glomerulonephritis, therapy with steroids, cytostatics and plasmapheresis is indicated.

Links

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- Glomerulonephritis
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- Rapidly progressive glomerulonephritis
- Chronic glomerulonephritis
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