Investigation of histological IgG4 staining and serum anti-PLA2R level in clinically primary and secondary membranous nephropathy

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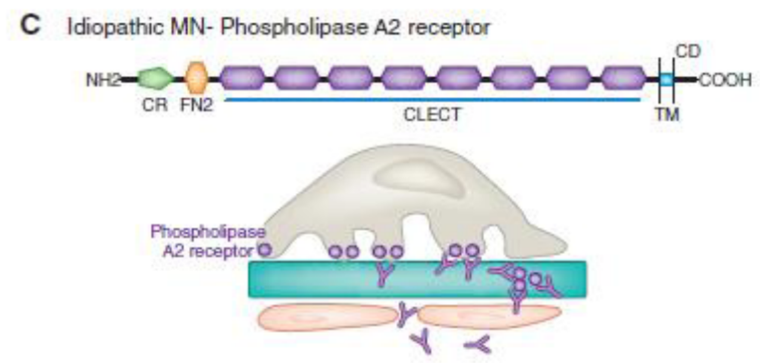
Primary membranous nephropathy in adults

In 70% of cases of primary membranous nephropathy (MNP) an antibody against a podocyte antigene (**M-type phospholipase A2-receptor, PLA2R**) can be detected in the serum which belongs to IgG4 subclass.



The role of the determination of serum M-type PLA2-R amtibody:

- confirms the primary origine of the disease
- shows the activity
- the therapeutical effect can be monitored
- if renal biopsy is contraindicated, it helps in the diagnosis

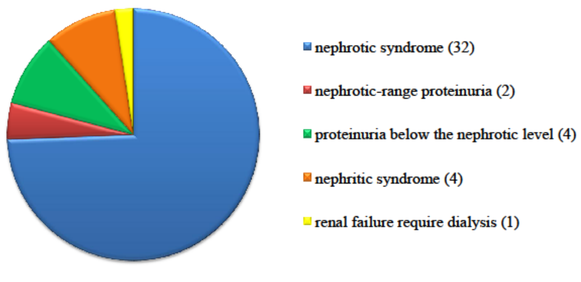
The histological IgG4 staining and serum anti-PLA2R positivity supports primary origine, yet it is essential to perform basic examinations to exclude secondary cause. It is especially important in in Central-Eastern Europe, because there is no sufficient data about the prevalence of antibody-connected MNP in this region.

Objectives

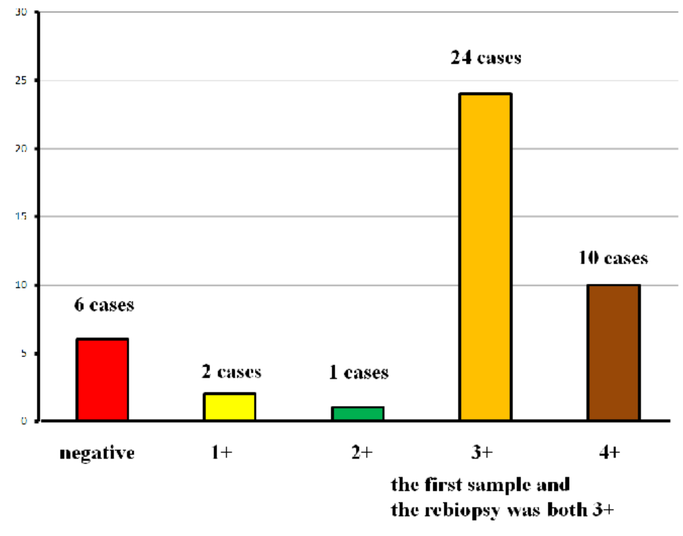
- to perform the posterior histological IgG4 staining of the stored renal biopsy samples of patients diagnosed with membranous nephropathy from 2007
- to evaluate if MNP was clinically primary or secondary
- the semiquantitative determination of serum anti-PLA2R level on follow-up and in same cases at the time of the diagnosis

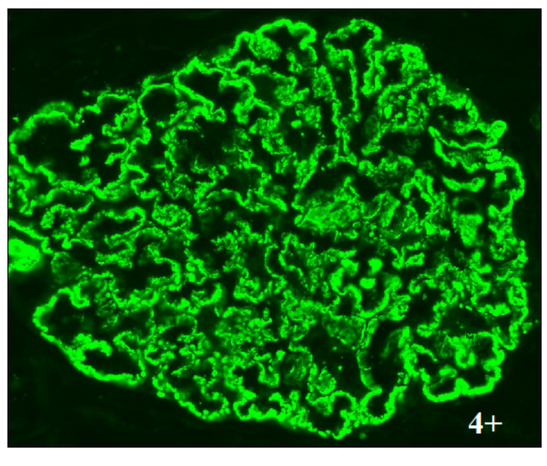
Clinical data of patients in the time of biopsy

- age: 50.4 15.3 years
- 14 males, 28 females
  (2 samples of 1 male – rebiopsy)



Histological IgG4 staining (negative, 1+, 2+, 3+, 4+)





IgG4 negative cases

3 cases: secondary origine was obvious (9 secondary cases from the 42 patients)
* in 2 - SLE
* in 1 – NSAID abuse

in 1 patient: the biopsy in 2007 was a rebiopsy
the 1st biopsy was in 1995, the rebiopsy (2007) showed a serious glomerulosclerosis
IgG4 negativity can be attributable to the „burn-out" disease

in 1 patient: diabetes was diagnosed but the disease clinically seemed to be primary (good response to immunosuppressive treatment)

in 1 patient: C1q-positivity and membranoproliferative signs emerged the possibility of SLE, but immunoserology did not support that and there were no other clinical signs of a systemic autoimmune disease

IgG4 positive cases

22 cases - definitely primary

6 cases - clinically secondary
- 1 patient: EBV infection, later chronic autoimmune hepatitis
- 1 patient: HbsAg positivity
- 1 patient: mixed connective tissue disease
- 2 patients: SLE
- 1 patient: rheumatoid arthritis, NSAID abuse

9 cases- clinically seemed to be primary, but secondary origine could not definitely excluded because of diabetes or comsumption of undetermined quantity of NSAIDs (in these latter cases it is difficult to differentiate between causality and coincidence)

Determination of serum anti-PLA2R level

In 31 patients – averagely after 35 (19) month follow-up

- in 4: serum anti-PLA2R positivity, primary cases clinically as well

IgG4 staining is positive as well

* in 1 patient: 57 months after the biopsy – in PR
* in 1 patient: 36 months after the biopsy – in active disease
* in 2 patient: 6 and 62 months after the biopsy – in relapse

- in the remaining 27 patients – serum anti-PLA2R negativity

the disease activity was clinically heterogene:
1- transplantated, 3 - no remission, 11- PR, 12 - CR

4 - IgG4 negative, 23 - IgG4 positive

7 clinically secondary, 14 clinically primary
in 6 the secondary origine was not definitely be excludable

In 6 patients – at the time or short after the time of biopsy (the disease was active in all cases)

- in 2 cases: strong antibody positivity
- in 4 cases: antibody negativity – among them just 1 was clinically obviously secondary (SLE)

These were all histologically IgG4 positive (3+ vagy 4+)

Conclusions

Histological IgG4 staining can help us to determine if MNP is primary or secondary, but it is still essential to screen for the most common secondary causes.

Serum anti-PLA2R positivity was only detected in 2 from 5 clinically primary cases, which can refer a smaller importance of this antibody in this region of Europe. Of course we need more data.

After 35 months average time of follow-up, the serum anti-PLA2R positivity – with histological IgG4 positivity – confirmed the primary origine, showed an active disease, but on the basis of the heterogene clinical picture and the heterogene histological IgG4 staining of serum antibody negative patients, the importance of the determination of serum anti-PLA2R level can not be definitely proved.

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