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Pernicious anemia and autoimmune polyendocrinopathy: a retrospective series

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ABSTRACT

Introduction: The objective of the study is to investigate the role of pernicious anemia among autoimmune polyendocrinopathy.
Methods: Retrospective and bi-centric study of 188 patients with pernicious anemia in order to search other autoimmune diseases and to evaluate the place of pernicious anemia in autoimmune polyendocrinopathy.
Results and Discussion: 74 patients with a combination of pernicious anemia – other autoimmune diseases were included in the study. Our series reveals the privileged association of pernicious anemia with autoimmune thyroiditis. The association pernicious anemia / autoimmune thyroiditis is a part of the autoimmune polyendocrinopathy type 3b.
Conclusion: On a practical level, we suggest undertaking a systematic clinical and laboratory investigation in search of an autoimmune thyroiditis in patient (s) with the diagnosis of pernicious anemia.

KEYWORDS pernicious anemia; autoimmune thyroiditis; autoimmune polyendocrinopathy;

Introduction:
A number of autoimmune diseases occur with high frequency in patients with pernicious anemia. They may precede or occur pernicious anemia at the discovery of the disease. The main objective of the study was to evaluate the role of pernicious anemia in autoimmune polyendocrinopathy.

Patients and methods:
Retrospective, multicenter study, including 188 observations of patients with a pernicious anemia, diagnosed and / or followed in several departments of Medicine in the University Hospitals of Reims and in the departments of Internal Medicine of the University Hospital of Strasbourg between January 2000 and December 2010. The records of 188 patients were studied retrospectively in search of autoimmune diseases associated with pernicious anemia.

Results and discussion:
74 patients with an association pernicious anemia - other autoimmune diseases were included (39, 4%). The average age was 61 years (25-98), 61 subjects (82.4%) were women; the sex ratio (male / female) was 0.2. Our study counted 74 cases of pernicious diseases associated with one or more autoimmune diseases. Our series reveals the privileged association of pernicious anemia with autoimmune thyroiditis with 57 cases (77%) with 12 patients suffering from Graves and 45 patients had Hashimoto thyroiditis, with a female predominance. The concomitant diagnoses pernicious anemia / autoimmune thyroiditis have been recorded for 23 cases. This association seems to be frequent, and observed also in a series of 78 patients with pernicious anemia, (Markson et al.) where they have noted a positive antithyroid antibodies in 33% of cases (1); another study by Doniach et al, on a series of 100 patients with positivity to 47% of cases (2). A pathogenetic link could exist between pernicious anemia and autoimmune thyroiditis, the main interest of our study lies in early detection. In our study, the diagnosis of pernicious anemia and autoimmune thyroiditis was most often concomitant. However, pernicious anemia is sometimes preceded the autoimmune thyroiditis several years ago. We believe, based on the results of our study, an evaluation of thyroid function should be performed routinely in a patient with pernicious anemia subject. And other studies raise the value of this early detection in both pernicious anemia patients and patients with autoimmune thyroiditis. A study by Nicolino - Peltier et al. on the detection of pernicious anemia in a group of 120 patients with autoimmune thyroid disease helped bring the probable diagnosis of pernicious anemia in pre stage -anemia in 8 patients of the 120 patients with autoimmune thyroiditis disease (including a balance sheet looking for anti- gastric mucosal antibodies, assay of gastrin and vitamin B12 by radioimmunoassay) (3). Morel et al, studied the prevalence of autoimmune thyroid disease and pernicious anemia combination by the presence of antiintrinsic factor antibodies in patients with autoimmune thyroiditis (113 patients); the sera of 113 patients were matched with 113 patients with non- autoimmune thyroid dysfunction. They found a prevalence of anti-intrinsic factor antibodies to 3.5%, being higher in patients with autoimmune thyroid disease than in those with non- autoimmune thyroid dysfunction (4).

Our study found a pernicious anemia / autoimmune diabetes combination in 23 (31 %) cases.

We find among these 23 associations, there are 15 cases where an autoimmune thyroiditis associated with it. Autoimmune diabetes is often associated with autoimmune thyroiditis; the prevalence of autoimmune thyroiditis varies from 15 to 30% of autoimmune diabetes (5) subjects. An estimated prevalence of pernicious anemia in patients with autoimmune diabetes was of 5 to 10% (5). A study by Perros et al., in 63 patients with autoimmune diabetes associated with autoimmune thyroiditis, was to determine the prevalence of pernicious anemia in these patients. The prevalence was estimated at 6.3 %, while the prevalence rises to 8.5% in women (6). This allows concluding that patients with both an autoimmune diabetes and autoimmune thyroiditis have amounted to develop pernicious anemia risk, which is confirmed in our study. Vitiligo was present in 9 subjects with pernicious anemia (12%).

Vitiligo appears to be the most represented skin disease (8), and this is what appears in our study. Our study is centered on the possible associations between pernicious anemia and other autoimmune diseases. Apart from pernicious anemia, vitiligo appears to be preferentially associated with autoimmune thyroiditis, preferential association as evidenced by the study of

Klisnick et al. (7).
We therefore find a preferential association pernicious / autoimmune thyroiditis, with a female predominance and a concomitant in 23 cases in our series. Pernicious anemia can be part of a large group that is the autoimmune polyendocrinopathy characterized by the coexistence of two or more en-

docrine deficiencies related to an autoimmune mechanism, sometimes associated with non-endocrine disease. (8) There is the type 1 of polyendocrinopathy, rare, affecting the small children, which is characterized by the coexistence of chronic candidiasis, hypoparathyroidism and acquired peripheral adrenal insufficiency. This is a monogenic autosomal recessive syndrome determined by mutations in the gene regulator autoimmunity AIRE (autoimmune regulator), recently identified on chromosome 21q22.3 (9). The AIRE gene is expressed in the thymus, lymph nodes, leukocytes, pancreas and adrenal cortex. It is a nuclear transcription factor whose mutations are the cause of a disruption of immune tolerance. The autoimmune polyendocrinopathy type

2 is characterized by a combination of primary adrenal insufficiency with thyroid disease carrying syndrome Schmidt and more or less a type 1 diabetes carrying the Carpenter syndrome in adults (9).The autoimmune polyendocrinopathy type 3 is characterized by the main syndrome which is autoimmune thyroiditis.It can either join an autoimmune diabetes (and more or less sarcoidosis or celiac disease) defining the autoimmune polyendocrinopathy type 3a; either pernicious anemia defining the type 3b ; either vitiligo and alopecia defining

3c. It differs from the type 2 by the absence of adrenal insufficiency. The association studied pernicious anemia / autoimmune thyroiditis is part of the autoimmune polyendocrinopathy type 3b (10). In both cases, it is polygenic syndromes with autosomal dominant transmission and incomplete penetrance. The presence of histocompatibility antigen HLA-DR3 is increased, especially the subtype DQB1.0102-DR3 (11). In our study, pernicious anemia is well integrated as follows. We noted five cases where pernicious anemia was associated with adrenal insufficiency, autoimmune thyroiditis and autoimmune diabetes (inconsistently), defining the type 2. What emerges from our study is that pernicious anemia fits more frequently in the autoimmune polyendocrinopathy type 3 with 30 associations pernicious anemia / autoimmune thyroiditis (defining the type 3b), 8 cases pernicious anemia autoimmune thyroiditis-autoimmune diabetes, 2 cases pernicious anemia-autoimmune thyroiditis-myasthenia, 3 cases pernicious anemia-autoimmune thyroiditis-autoimmune diabetes-vitiligo, one case pernicious anemia-autoimmune thyroiditis-vitiligo, 2 cases

pernicious anemia-autoimmune thyroiditis-Gougerot-Sjogren, 1 case pernicious anemia autoimmune thyroiditis-antiphospholipid syndrome. Autoimmune thyroiditis is the cornerstone of type 3 autoimmune polyendocrinopathy.

The HLA locus is the main example of participation in a common genetic background with a large number of autoimmune diseases. HLA molecules are encoded by the major histocompatibility complex on chromosome 6 and are essential in the immune system, playing a central role in antigen presentation to T cells. For most autoimmune diseases, HLA is to date the genetic factor with the greatest weight in the genetic component with a relative risk ranging from 8 to 20. (12) (13). Thus, HLA associations and disease is the link that unites the various autoimmune diseases (11). And pernicious anemia has an association with HLA- DR5 for a relative risk of 5 , Hashimoto's thyroiditis partnering with the HLA- DR3 to a relative risk of 3.2 and HLA- DR5 for a relative risk 5,8 (14), the autoimmune diabetic subjects , 90% of the Caucasian population associated with HLA DR3 and / or DR4 (5). Haplotypes risks Hashimoto's thyroiditis are HLA DQ A1 * 0301 linked to DR4, DQB1 * 0301 associated with DR5 and DQB1 * 0201 linked to DR3 (10). The haplotype DR3- DQB1 * 0201 contributes to genetic susceptibility to type 1 diabetes, autoimmune thyropathy and polyendocrinopathy 2 and 3 (9). A genetic predisposition has been suggested for pernicious anemia. In type 1 diabetic subjects, a weak association between pernicious anemia and HLA haplotype DQA1 * 0501 -B1 * 0301, HLA- DR5 bound was observed (5). Patients with pernicious anemia association and autoimmune endocrine diseases often have DR3/DR4 genotype. Autoimmune thyroiditis/ pernicious anemia is part of a typical polyendocrinopathy 3b for which a predisposition genetic (HLA- B8 and / or DR3 and DR5) seems important. These data support the involvement of the DR3 haplotype in susceptibility to autoimmune diseases. HLA DR3 could be a thread in immunogenetics association of various autoimmune diseases in autoimmune polyendocrinopathy.

Conclusion:
This association (pernicious anemia - autoimmune thyroiditis) is not fortuitous. We suggest a systematic clinical and laboratory investigation in search of an autoimmune thyropathy in patient (s) with the diagnosis of pernicious anemia. Similarly, a patient with autoimmune thyroid disease should be regularly monitored for several years to detect as soon as possible an autoimmune disease such as pernicious anemia.

Conflict of interest: None for this work

Sponsor's role: None

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