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Thyroid gland involvement in Henoch-Schönlein purpura

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Abstract

With an estimated overall prevalence of 10%, thyroid disorders are among the most common endocrine pathologies. Autoimmunity plays a crucial role in the majority of cases of thyropathies explaining the frequent association of these dysthyroidism with other systemic and/or organ-specific autoimmune diseases or systemic vasculitis. Apart from this autoimmune vasculitis, thyroid disorders remain exceptional during other systemic vasculitis including Henoch-Schönlein's purpura.

The purpose of this paper is to discuss the clinical presentations and possible pathogenic mechanisms of thyroid dysfunction during this systemic angiitis.

Keywords: Henoch-Schönlein's purpura, Henoch-Schönlein's syndrome, Thyroid gland, Thyroiditis, Vasculitis, Angiitis

Introduction

With an estimated overall prevalence of 10% [1], thyroid disorders are among the most common endocrine pathologies and are often primary due to damage to the thyroid gland itself [2-6].

Hypothyroidism is the most common clinical presentation of these disorders; the prevalence of free (symptomatic) forms is of the order of 1 to 5% of the general population with an annual incidence between 1 and 2 ‰ for women and 0.2 ‰ for men [7]. Subclinical (asymptomatic) forms are by far more frequent and their prevalence can be as high as 20% in the elderly [8,9].

Autoimmunity plays a crucial role in the majority of cases of thyropathies (Hashimoto autoimmune thyroiditis, Graves' disease, postpartum lymphocyte thyroiditis, Riedel fibrous thyroiditis, DeQuervain sub acute thyroiditis, etc.) [10] thus explaining the frequent association of these dysthyroidism with other systemic and/or organ-specific dysimmune diseases [10,11], including autoimmune systemic vasculitis such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis [12,13], cryoglobulinemia [14], and vasculitis of connective tissue [10,11]. The common dysimmunitary signature is at the base of the pathogenesis of the two affections.

Apart from this dysimmune vasculitis, thyroid disorders remain exceptional during systemic vasculitis [15-17]. They are mostly reported in association with vasculitis of small vessels suggesting a direct involvement of the glandular parenchyma by the inflammatory vasculitic process [12,13].

Henoch-Schönlein syndrome (HSS) or Henoch-Schönlein purpura is currently recognized, according to the International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC)) of 1994 revised in 2012 [18], as a leukocytoclastic vasculitis of small vessels caliber with predominant cutaneous, digestive, and renal localizations and endovascular deposits of immunoglobulin A (IgA) features [18].

The thyroid lesions during HSS are little reported and little studied. The purpose of this paper is to discuss the clinical presentations and possible pathogenic mechanisms of thyroid dysfunction during HSS.

Henoch-Schonlein purpura

Henoch-Schönlein syndrome (HSS) or Henoch-Schönlein purpura, better still "systemic IgA vasculitis" according to the new nomenclature of systemic vasculitis of Chapel Hill [18] is a primitive systemic vasculitis with circulating immune complexes of the vessels of small caliber which is characterized by the presence of immune deposits (CIC) made of IgA in the affected tissues (skin, kidneys, vessels, other viscera ...); it is particularly common in children between 4 and 5 years of age, with an annual incidence ranging from 6.1/100,000 to 20.4/100,000 depending on the series and ethnic groups [19,20]. It remains exceptional in adults: the disease is 20 times rarer in adults than in children [21].

Its diagnosis is mainly based on the criteria of the American College of Rheumatology (ACR) 1990 [22] (Figure-1), and more recently the criteria of the European League against Rheumatism/ Pediatric Rheumatology International Trials Organization/ Pediatric Rheumatology European Society (EULAR / PRINTO / PRES) for pediatric vasculitis [23] (Figure-2).

The sensitivity of these diagnostic criteria is 87% and their specificity is 88% [19,20], but the age criterion (often less than

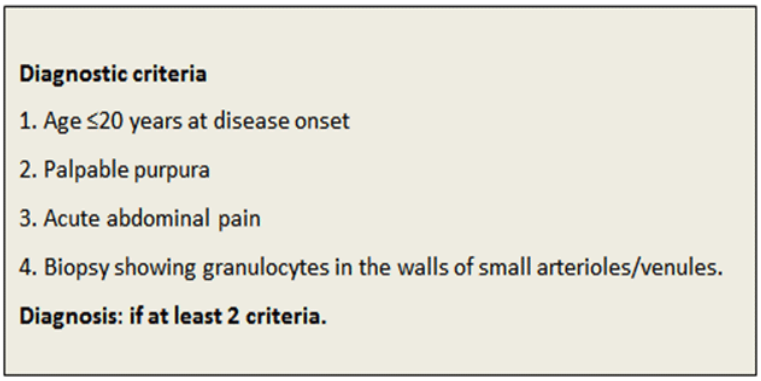

Figure 1: The American College of Rheumatology (ACR) 1990 criteria for Henoch–Schönlein purpura diagnosis

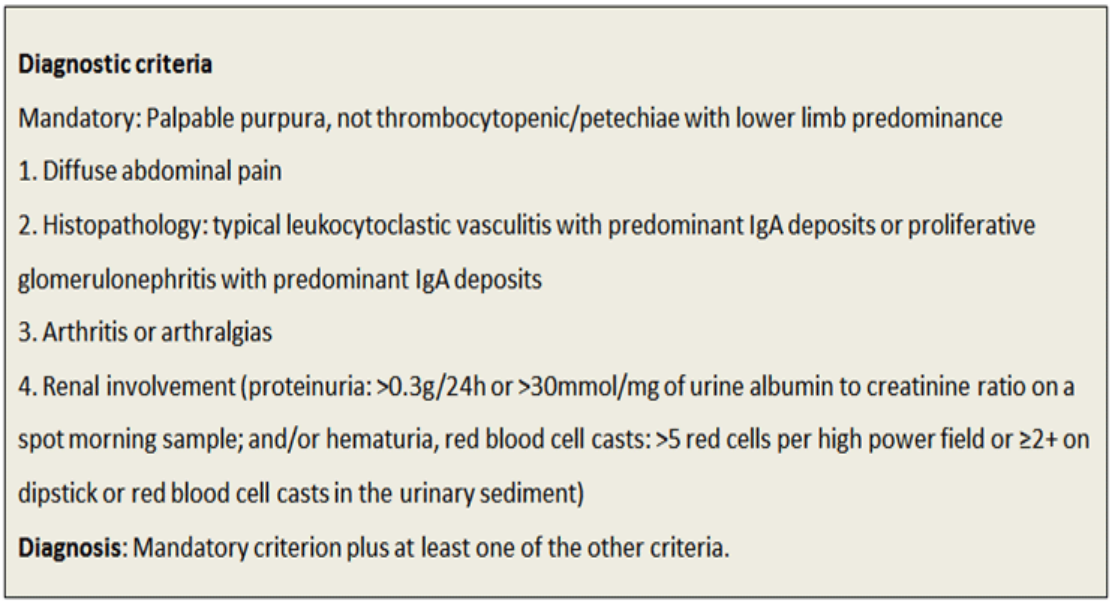

Figure 2: European League against Rheumatism/Pediatric Rheumatology International Trials Organization/Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) 2010 criteria for Henoch–Schönlein purpura diagnosis.

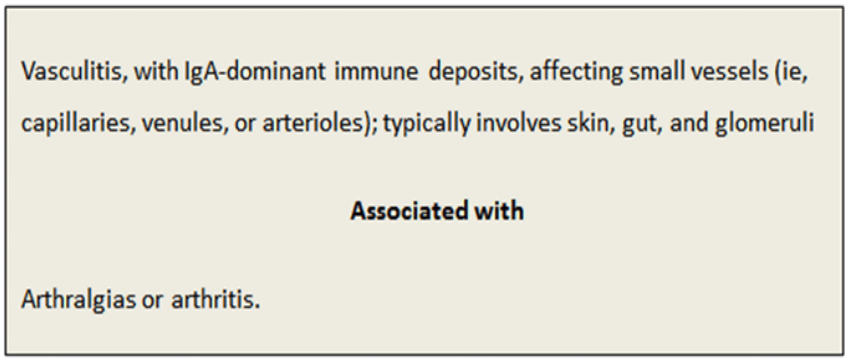

Figure 3: 1994/2012 Chapel Hill Consensus Criteria for Henoch–Schönlein purpura diagnosis.

20 years) represented the main limitation for their application in adults; the definition/criteria of Chapel Hill consensus conference on nomenclature of systemic vasculitis thus seems more suitable [18] (Figure-3).

Endocrine involvement in HSS

The involvement of the endocrine glands is unusual during HSS, and apart from the testicular involvement often included in that of the external genital organs (orchitis and epididymitis ..) which is common during this vasculitis [24,25], there have been sporadic cases of ovarian [26], adrenal [27,28], pituitary [27], and endocrine pancreas involvement with type 1 diabetes in a nine-year-old child [29]. Regarding the thyroid gland, less than a dozen cases of autoimmune thyroiditis have been reported in association with HSS in the form of sporadic cases in both children and adults [30-33].

Thyroid gland involvement in HSS

Thyroid involvement in HSS remains exceptional and is largely dominated by Hashimoto's hypothyroidism of chronic thyroiditis. The mechanism of this association is dys-immune; mainly incriminating CIC deposits [30-34].

More rarely, it may be a combination of SSH with Graves' disease or a direct dys-immune mechanism or induced by synthetic anti-thyroid drugs [35-37]. Exceptionally other types of thyropathies have been reported during or in association with HSS without the pathogenetic mechanism promoting is elucidated, we note:

- The observation of Negri M et al, associating HSS with thyroid adenocarcinoma [38],
- The observation of Kim S et al, associating HSS with lymphocytic thyroiditis in a 72-year-old woman who also had rheumatoid arthritis [39],
- The observation of Oner A et al, associating an SSH with a sub-acute thyroiditis of De Quervain in a child of 12 years [40],
- Thomas RM et al, presented at the 96th annual meetings of the American Endocrinology Society in Chicago (Endocrine Society's 96th Annual Meeting and Expo, June 21-24, 2014 - Chicago) an anecdotal case of HSS associated with Graves' disease at the same time and metastatic papillary carcinoma of the thyroid. The diagnosis of Graves' disease was made initially, then one week after that of HSS, then two weeks after that of thyroid cancer [41],
- Exceptionally, hypothyroidism may be a complication of HSS treatment with dapsone (Disulone®) [21] or Graves' disease may be induced by cyclosporine prescribed to treat severe HSS nephropathy [37].

A historical paper published in JAMA in 1907 by Robinson J Wiret exposed an original case of HSS occurring in a six-year-old child resistant to different treatments of the time. The author had the idea to put it under thyroid extracts (because of their effects on the basic metabolism in a general way) with an extraordinary evolution. In addition, three successive recurrences of HSS were perfectly controlled by the thyroid extracts alone [42].

Mechanisms of thyroid involvement during HSS

A dys-immune mechanism common to these two conditions (autoimmune thyroiditis and HSS), mainly via the deposition of CIC containing IgA (which characterize HSS) is strongly evoked [34]. These CIC deposits at the level of the glomeruli, the dermal-epidermal junction, as well as at the level of the basement membrane of the thyroid epithelium could explain the simultaneous occurrence of these two affections [34].

In favor of this dys-immune mechanism of the association, we retain:

- The association with HSS to other autoimmune diseases with organ-specific auto antibodies, such as rheumatoid arthritis, systemic lupus erythematosus, primary Sjögren's syndrome, granulomatosis with polyangiitis, cryoglobulinemia and cryptic inflammatory bowel diseases [33],
- A case of Hashimoto thyroiditis associated with HSS occurring during pregnancy in a 27-year-old woman [32],
- Siddiqui Z et al reported an interesting observation of a 36-year-old hypothyroid woman who was well balanced for more

than five years under the same dose of levothyrox (75µg/d), and who suddenly became very ill-balanced with recovery of clinical signs of hypothyroidism requiring an increase in daily doses up to 200µg without improvement. On clinical examination, she had a petechial purpura of both lower limbs with biology acute renal failure, anemia 8g/dl and proteinuria at 5.6g/24h. Cutaneous and renal biopsies concluded with SSH with classical IgA nephropathy. Simultaneously, its TSH was raised to 560ml/l with anti-TPO auto antibodies positive at 690 ml/ml (normal <100). After corticosteroid therapy at a dose of 60 mg/day for HSS, there was a marked improvement in thyroid function with the same reduction in the daily dose of levothyroxine at 150µg/day. It was therefore a reactivation of Hashimoto's thyroiditis during an HSS surge confirming once again the non-hazardous association of these two pathologies as well as the common pathogenetic dys-immune signature [34],

- Similarly, some cases of Graves' disease (other autoimmune thyroiditis) have been reported in association with HSS [35-37].

The mechanisms were multiple

- HSS induced by treatment with propylthiouracil (PTU) of Graves' disease at usual doses [35] or during an overdose of the drug [36],
- Graves' disease occurring after cyclosporine A treatment for HSS with severe renal impairment [37].

These associations suggest that irrespective of the possible involvement of synthetic antithyroid drugs (PTU and PTU-induced ANCA-associated vasculitis), HSS and Graves' disease (and more generally autoimmune thyroiditis) share a predisposing genetic background as well as a common dys-immune signature [35,37].

The richness of the arterial blood supply of the thyroid gland making it a preferred theoretical target of vascular inflammation during systemic vasculitis, may suggest the hypothesis of a direct attack of the thyroid by the HSS (thyroid vasculitis) ; no case has been proven histologically. This hypothesis is comforted by the objectification of true thyroid vasculitis and/or other endocrine glands proven histologically during other systemic angiitis [12,13]. The reduction of the thyroxin dose necessary to compensate for thyroid hormone deficiency after adapted corticosteroid therapy of HSS, as well as the temporal concordance of flares of vasculitis and hypothyroidism in the observation of Siddiqi Z et al plead in favor of this hypothesis [34].

Conclusion

Although, rare and very little known, the involvement of the thyroid gland during HSS seems to be far from a simple hazard. The most common associations are with autoimmune thyroiditis, especially Hashimoto's thyroiditis and Graves' disease suggesting a similar predisposing terrain and a common autoimmune signature. Other thyropathies remain exceptional. The direct involvement of the thyroid gland with HSS-specific vascularity, although highly plausible due to the richness of the thyroid vasculature, has not been proven histologically.

It thus seems useful to carry out a screening of the thyroid functions, and particularly of the thyroid autoimmunity, in any patient followed for HSS in order to early detect any associated thyroid dysfunction and treat it in time.

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