intracellular lymphoid tyrosine phosphatase (LPY) with negative regulatory effects on T-cell activation.27

In a cohort of 60 Tunisian patients with high incidence of autoimmune thyroid disease and type 1 diabetes, some non-HLA autoimmunity genetic factors were demonstrated as contributors to autoimmune polyglandular syndrome type 2.28 In Japanese patients with thyroid autoimmune disease (AITD) and type 1 diabetes (TD1) defined as autoimmune polyglandular syndrome type 3, a female predominance, a slow and older age onset of T1D and a higher prevalence of anti-GAD were observed, compared to T1D without AITD. Differences between the two groups may reflect distinct genetic backgrounds including the HLA DRB1-DQB1 haplotypes and CTL4 gene polymorphisms.29

Table 4 summarizes prevalence of the main features of the PEA2: autoimmune thyroid diseases, diabetes, Addison, gonadal insufficiency with premature ovarian insufficiency, vitiligo, alopecia and pernicious anemia. Testicular failure is rare.

In the recent series of 125 cases summarized by G Kahaly,4 the most frequent combinations were type 1 diabetes and AITD in 41%, AITD and Addison’s disease (the Schmidt syndrome) in 15%, followed by diabetes + vitiligo or AITD + vitiligo in 10%.

A long period between cellular loss and overt autoimmune disease is observed. At this time, circulating antibodies can be detected, aiding in assessment of the risk of the endocrine emergency. The shortest interval is between Addison and AITD, the longest between diabetes or vitiligo and thyroid diseases. It is noteworthy that almost 70% of the patients with Addison have a concomitant autoimmune thyroiditis.

In daily practice, some high-risk associations have to be underlined: e.g diabetes and Addison, type 1 diabetes and hypopituitarism, since patients have a higher risk of hypoglycemia.

Hypothyroidism can determine disorders of growth disorders, but this raises the question of growth hormone (GH) deficiency. Treatment with GH of patients suffering from hypopituitarism leads to disclosure of some central hypothyroidism, or else modifies the need for substitutive doses of levothyroxine.30,31 Hypothyroidism reduces the need for insulin and can be responsible for hypoglycemia. Since thyroxine replacement enhances cortisol clearance, correction of hypothyroidism can precipitate adrenal crisis in patients with subclinical adrenocortical failure. Finally, high TSH levels are common in patients in whom adrenal insufficiency is discovered and may sometimes be corrected with hydrocortisone supplementation.32-34

Graves’ disease induces determines glucose intolerance and coincides with diabetes in 3% of cases. Hyperthyroidism can also be revealed by an acute disequilibrium of Addison’s disease.4

An unrecognized endocrine disorder, mainly autoimmune thyroiditis, is observed in about 1 in 7 first degree relatives of patients with PEA2,35 thus routine screening of TSH measurement should be seriously considered in this population. However, genetic typing is neither really efficient nor recommended, since PEA2 is polygenic and multifactorial.

**IPEX SYNDROME (IMMUNODYREGULATION POLYENDOCRINOPATHY ENTEROPATHY X-LINKED SYNDROME)**

The IPEX syndrome is even rarer than the APECED syndrome. It appears in very early childhood in males. The disorder manifests with psoriasisform or eczematous dermatitis, nail dystrophy, autoimmune skin conditions such as alopecia universalis, bullous pemphigoid, food allergy, infections and severe enlargement of the secondary lymphoid organs and, lastly, autoimmune endocrinopathies: insulindependent diabetes, hypothyroidism.36 Transmission is monogenic, related to the FOXP3 gene which codes for the scurfin protein.37 Scurfin is a transcriptional activator factor which has a key role