0021-972X/98/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 83, No. 4
Printed in U.S.A.

CLINICAL REVIEW 93

Autoimmune Polyglandular Syndrome Type 1

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THE FIRST description of the association between hypoparathyroidism and candidiasis was published in 1929 (1), and the association of these two diseases with idiopathic adrenal insufficiency was reported in 1946 (2). Autoimmune polyglandular syndrome (APS) type 1 has been described under other names, such as Whitaker's syndrome (3), polyglandular autoimmune disease type 1 (4, 5), or autoimmune polyendocrinopathy, candidosis, ectodermal dystrophy (6).

Prevalence

APS type 1 is a very rare disorder. In Finland, where the highest number of patient groups with APS type 1 has been reported, the estimated prevalence is about 1 in 25,000 inhabitants. In the majority of the cases, the syndrome occurs in childhood (3–5). The female/male ratio varied in the different reports from 0.8–1.5 (see Table 1). In Italy, only a few case reports (7–10) or small groups of patients (11, 12) have been described to date.

From 1967 to 1996, we studied 41 patients with APS type 1, 24 of whom were followed up for 1–25 yr; 15 came from the Veneto region, and of these, 9 were from the area of Vicenza. In all patients, data about the presence of autoimmune diseases and the age of presentation were collected; 1 or more serum samples were tested for organ- and non-organ-specific autoantibodies, and in 17 cases, a genetic study was also performed.

Immunogenetics

APS type 1 is a condition that may occur sporadically or among siblings (4, 5, 13–15). In the early studies no association with human leukocyte antigen (HLA) class I or II antigens was found (16). Subsequently, HLA-A28 was demonstrated to be more frequent in patients with APS type 1 than in normal controls, and HLA-A3 was more frequent in those with APS type 1 and ovarian failure than in those with normal ovarian function (17). In the study of 14 families with APS type 1, an association between the clinical expression of the syndrome and genes located in chromosome 21 has been identified (18). The gene for APS type 1 has been recently cloned, and the mutation R257X was shown to be responsible for 82% of Finnish APS type 1 alleles (19).

Received August 13, 1997. Revision received October 20, 1997. Accepted November 24, 1997.

In our series, 3 family groups with this syndrome were identified. In 17 patients, HLA class I (A, B antigens) analysis revealed no significant differences from normal controls, whereas HLA class II (DR genes) analysis revealed an increased frequency of DR3 (relative risk, 1.84) and DR5 (relative risk, 2.85). In cooperation with Dr. H. Scott, University of Geneva (Geneva, Switzerland), we studied 5 of our patients, and the mutation R257X was found in 4 of them.

Clinical aspects

The major components of APS type 1 are chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and autoimmune adrenal insufficiency (Table 1). To define this syndrome, at least two of these diseases have to be present in one individual (4, 5, 6, 13, 20).

The spectrum of associated minor clinical diseases include other autoimmune endocrinopathies (hypergonadotropic hypogonadism, insulin-dependent diabetes mellitus, autoimmune thyroid diseases, and pituitary defects), autoimmune or immuno-mediated gastrointestinal diseases (chronic atrophic gastritis, pernicious anemia, and malabsorption), chronic active hepatitis, autoimmune skin diseases (vitiligo and alopecia), ectodermal dystrophy, keratoconjunctivitis, immunological defects (cellular and humoral), asplenia, and cholelithiasis (Table 1) (4, 5, 6, 13, 20).

In general, the first manifestation usually occurs in the childhood, and the complete evolution of the three main diseases takes place in the first 20 yr of life, whereas other accompanying diseases continue to appear until at least the fifth decade (5, 6). In a majority of cases, candidiasis is the first clinical manifestation to appear, usually before the age of 5 yr, followed by hypoparathyroidism (usually before the age of 10 yr), and later by Addison's disease (usually before 15 yr of age) (4, 5, 6, 15). Overall, the three main components of APS type 1 occur in a fairly precise chronological order, but they are present together in only about one third to one half of the cases (4–6, 15). It has been reported that the earlier the first component appears, the more likely it is that multiple components will develop; conversely, patients who have late manifestations of the disease are likely to have fewer components (5, 6).

In our series of 41 patients, the first manifestation of APS type 1 was observed in 37 patients (90%) in childhood and 4 (10%) in adulthood at a mean age of 7.4 yr (range, 1–37 yr). The female/male ratio was 2.4. Twenty-one patients (51%)

TABLE 1. Clinical manifestations of APS type 1

	Authors		
	Neufeld 1981	Ahonen 1990	Present report 1998
No. of cases	71	68	41
Female/male	1.5	0.8	2.4
Deceased		9	4
Familial APS (%)		13.2	17.5
Main manifestations (%)			
Chronic hypoparathyroidism	76	79	93
Chronic candidiasis	73	100	83
Autoimmune Addison's disease	100	72	73
Minor manifestations (%)			
Autoimmune hypergonadotropic hypogonadism	17	50	43[a]
Alopecia	32	29	37
Chronic hepatitis	13	12	20
Chronic atrophic gastritis	13	13	15
Pernicious anemia	13	13	15
Vitiligo	8	13	15
Malabsorption	22	18	15
Sjögren's syndrome			12
Autoimmune thyroid disease	11	2	10
Keratoconjunctivitis		35	12
Hypophysitis			7
Turner's syndrome			2
IDDM	4	12	2
Hemolytic anemia			2
Vasculitis		3	2

[a] Frequency calculated on 21 patients over the age of 14 yr.

had all 3 main diseases, 20 (49%) had 2 of them (11 candidiasis and hypoparathyroidism, 6 Addison's disease and hypoparathyroidism, 3 candidiasis and Addison's disease). A combination of 2–9 different diseases could be found in these patients; those with 2 or 3 diseases developed the first at a mean age of 10 yr, and those who had more than 3 diseases developed the first at a mean age of 6 yr.

The clinical manifestations of APS type 1 and their prevalence in different groups of patients studied, including our own series, are summarized in Table 1.

Major clinical manifestations

Chronic mucocutaneous candidiasis (CMC). CMC generally presents earliest in life and is the most frequent of the three main diseases of APS type 1. It can appear as early as at the first month after birth up to 21 yr of age, with a peak of occurrence in early childhood (4–6, 15, 20). CMC is present in 73–100% of all patients (4–6, 15); it affects the nails, the dermis, and the oral, vaginal, and esophageal mucous membranes. In the majority of cases, the infection is limited to not more than 5% of the skin surface (6). In rare cases, this disorder can cause important complications; for example, Ahonen described 4 cases of esophagitis, with esophageal stricture in 1 patient, and 11 other cases with periodical retrosternal pain that resolved with oral antifungal therapy (6). CMC is considered the clinical expression of an immunological selective T cell deficiency with an inability to respond *in vivo* and *in vitro* to candidal antigens (4, 11, 21–24). However, these patients, in general, have a normal B cell response of serum antibodies to candidal antigens, which is considered important in preventing the development of systemic candidiasis (24). For this reason, APS type 1 is also classified as an acquired immunodeficiency (25).

CMC was present in 34 of 41 (83%) of our patients. The age at onset ranged from 1–36 yr (mean, 6.5 yr; Fig. 1). CMC was the first manifestation of the syndrome in 93% of the cases. One patient, after 25 yr of follow-up, developed esophageal stenosis due to CMC, another subject died of a general candidal infection at 13 yr of age after immunosuppressive therapy. Periodical antifungal treatment is required in patients affected by CMC. We have treated 2 patients with itraconazole according to protocol suggested by DePadova-Elder (26) with good results in the case of nail infection. As CMC is most often the first manifestation of APS type 1, it can be considered a precocious marker of APS type 1. Consequently, all patients affected by isolated CMC, especially children, should be evaluated and carefully followed up by immunological, biochemical, and clinical tests to recognize signs and symptoms of imminent or ongoing endocrine glandular failure.

Hypoparathyroidism and parathyroid autoantibodies. Chronic hypoparathyroidism is the first endocrine disease to occur during the time course of APS type 1 (4–6, 13, 20), usually after CMC and before Addison's disease, and can present between 3 months to 44 yr of age (mean, 7.5 yr). During the neonatal period, it is important to distinguish autoimmune hypoparathyroidism from the cases of absence, maldescent, or maldevelopment of the parathyroids with variable degrees of thymic hypoplasia, the so-called Di George's syndrome. Chronic hypoparathyroidism has been reported in 73–90% of the cases of APS type 1 (4–6, 15). In the past, many of these patients died, and at autopsy, parathyroid tissue was atrophic or not detectable (3, 13).

Parathyroid autoantibodies, detected by an indirect immunofluorescence technique (IIT), have been described in 11–38% of the patients with hypoparathyroidism (27, 28). Studies in several other laboratories have been unable to confirm these first results, but demonstrated that some patients reacted with parathyroid oxyphilic cells rich in mitochondria, and these reactivities could have been responsible for the early reports (29, 30). Subsequently, IIT studies indicated that 33% of patients with sporadic adult-onset hypoparathyroidism had autoantibodies reacting with the surface of dispersed human parathyroid cells or parathyroid sections and inhibiting PTH secretion by these substrates (31). Cytotoxic autoantibodies reacting with cultured bovine

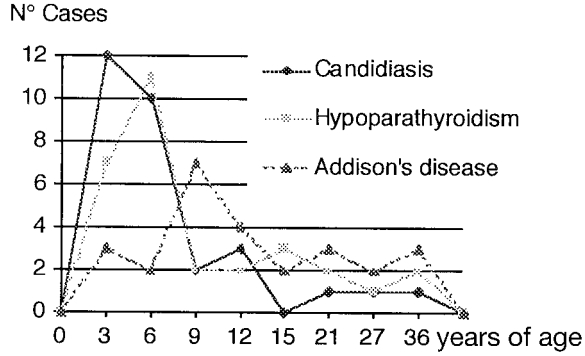

FIG. 1. Timing of major clinical features in APS type 1.

parathyroid cells were also found in all sera (32), but these antibodies lost their reactivity after absorption with endotelial cells (33). Recently, autoantibodies to the extracellular domain of the calcium-sensing receptors, evaluated by immunoblot analysis, have been demonstrated in the sera of 56% of patients with acquired hypoparathyroidism, most of whom had APS type 1 (34).

Hypoparathyroidism was present in 38 of 41 (93%) of our patients. The mean age of onset was 9.2 yr (range, 2–36 yr; Fig. 1). None of the 35 patients with APS type 1 and hypoparathyroidism studied by us revealed a specific reactivity against cryostat sections of parathyroid tissue by IIT, whereas 13% presented human mitochondrial autoantibodies, as previously reported (30).

Addison's disease and antibodies to steroidogenic enzymes. Autoimmune Addison's disease (AAD) is usually the third disease to appear during the time course of APS type I, usually between 6 months and 41 yr of age, with a peak around the age of 13 yr (4–6, 15). AAD occurs in 60–100% of cases of APS type 1 (4–6). In the past, many of these patients died, and at autopsy, adrenal tissue was atrophic, the normal architecture of the adrenal-cortex was completely distorted and almost destroyed, and the remaining cortical cells were dispersed in the fibrous tissue in small clusters. A prominent feature was extensive mononuclear cell infiltration with small lymphocytes, plasma cells, and macrophages. In some cases the adrenal medulla was also atrophic (13).

In patients with AAD in the context of APS type 1 adrenal cortex autoantibodies (ACA), detected by IIT, varied according to the duration of the disease from 100% at diagnosis to 78% 8 yr after disease onset (35). In addition, steroid-producing cell autoantibodies (StCA) were demonstrated in 81–100% of ACA-positive patients (36). StCA were always associated with ACA and were generally considered serological markers of hypergonadotropic hypogonadism (35–37).

Initial studies of autoantigens recognized by autoantibodies in sera from patients with AAD in the context of APS type 1 have given conflicting results. Steroid 17α-hydroxylase (17α-OH) was the first autoantigen reported to be involved (38); subsequently, P450 side-chain cleavage (P450scc; desmolase) was also identified (39, 40), and finally, steroid 21-hydroxylase (21-OH) was included in the family of target autoantigens (41–43). In 1994, Uibo *et al.* (42) reported that sera from patients with AAD associated with APS type 1 reacted with at least one of the three above-mentioned autoantigens, and this observation was supported by a later study (44). In contrast, Chen *et al.* (45) reported that in APS type 1, ACA recognized 21-OH as major autoantigen, whereas StCA recognized other autoantigens, such as 17α-OH and/or P450scc. To date, although there appears to be some disagreement about the main autoantigen in APS type 1, there is a consensus that 21-OH is the major autoantigen in APS type 2 and isolated AAD (46).

In our series, Addison's disease developed in 30 of 41 (73%) of the patients at a mean age of 13.6 yr (range, 2–37 yr; Fig. 1). ACA were found in 93% of our patients (94% with recent-onset Addison's disease and 92% studied at least 3 yr after diagnosis). StCA were present in 55% of the ACA-positive patients independently of the duration of the disease.

ACA can also be detected in patients with APS type 1 in the absence of clinical AAD (47, 48). We studied 20 patients with candidiasis and hypoparathyroidism initially without AAD, and 11 (55%) were found to be ACA positive. Nine of these patients were followed up and assessed by ACTH test; 8 developed clinical and 1 subclinical AAD after a mean follow-up period of 30 months (range, 3–121 months) (49, 50). These data indicate that subjects with chronic candidiasis and hypoparathyroidism should be tested for ACA and, if positive, carefully followed up because of the high risk of fast progression to clinical AAD.

To identify the autoantigens recognized by APS type 1 sera, in collaboration with Dr. J. Furmaniak (FIRS Laboratories, RSR, Cardiff, Wales) we studied 26 of these patients with or without AAD and premature ovarian failure and confirmed a strong association between ACA detected by IIT and 21-OH autoantibodies detected by immunoprecipitation assay (IPA) and between StCA detected by IIT and 17α-OH and/or P450scc autoantibodies detected by IPA (Table 2).

On the basis of these results, it seems likely that the sharp dichotomy in autoantigen recognition in APS type 1, hypothesized by others, can be explained by the presence or absence of StCA in addition to ACA.

Minor clinical manifestations

Autoimmune endocrinopathies.

Hypergonadotropic hypogonadism: APS type 1 is associated with hypergonadotropic hypogonadism in 17–50% of the cases, and all affected patients are StCA positive (4–6, 15, 36, 37). Gonadal failure can occur before the age of 40 yr (secondary amenorrhea) or even before the normal age of puberty (primary amenorrhea) (37). The gonadal tissues, studied in some of these cases, showed hypoplasia and lymphocytic infiltration of the developing ovarian follicles (13, 37, 46).

StCA have also been described in patients with APS type 1 in the absence of hypogonadism, and the follow-up of these patients revealed the evolution toward hypergonadotropic hypogonadism only in females (51, 52).

In our series, of 21 patients over 14 yr of age (15 females and 6 males), 6 females had hypergonadotropic hypogonadism; 5 of them (83%) were StCA positive, and the remain-

TABLE 2. ACA, StCA, and auto-antibodies to cytochrome P450 enzymes in 26 patients with APS type 1 with or without AAD or POF

IIT pattern	No. of patients	IPA based on recombinant P450 enzymes		AAD	POF
		21-OH Abs	17α-OH Abs and/or P450scc Abs		
$ACA^+/StCA^+$	14	14	13	13	4
$ACA^+/StCA^-$	5	4	1	4	0
$ACA^-/StCA^-$	7	0	0	3	0

21-OH, 21-hydroxylase; 17α-OH, 17α-hydroxylase; P450scc, P450 side-chain cleavage, IIT, indirect immunofluorescence technique; IPA, immunoprecipitation assay; AAD, autoimmune Addison's disease; POF, premature ovarian failure.

ing subject was affected by Turner's syndrome. None of the males had hypergonadotropic hypogonadism. StCA were also found in 10 of 15 (67%) patients over 14 yr of age without hypogonadism, and the disease developed in 3 of 6 (50%) StCA-positive females after a mean period of 12 yr, but in none of the 4 males. These data emphasize the strong association between autoimmune hypogonadism due to lymphocytic oophoritis and StCA.

Insulin-dependent diabetes mellitus: Insulin-dependent diabetes mellitus (IDDM) has been described in 1.2–12% of patients with APS type 1 (4–6, 15), most of them had islet cell (ICA) and/or glutamic acid decarboxylase (GAD-Abs) autoantibodies (53). ICA were also found in 18–28% of APS type 1 patients without IDDM (53). In addition to GAD Abs, antibodies to a novel 51-kDa antigen (51-kDa Ab) of the islet cells, were found in all six sera studied without IDDM (54). This 51-kDa Ab was subsequently identified as L-amino-acid decarboxylase (55). Depletion of the GAD protein from the islet lysate did not affect the amount of 51-kDa Ab, demonstrating that the latter is unrelated to GAD (54).

On the basis of the high frequency of GAD and/or ICA in APS type 1 and the low risk of IDDM in this population, some researchers reported that patients with APS type 1 have antibodies reactive with different epitopes of GAD_{65} compared to those in patients with IDDM (56). It has also been suggested that these antibodies are markers of a subclinical inflammatory process in the pancreas that does not invariably progress to clinical diabetes (53).

In our series, the only patient (2.5%) who presented with IDDM was ICA negative. However, ICA were found in 12 of 40 (30%) patients without IDDM; the majority of them were also positive for GAD_{65} Abs. In collaboration with Prof. O. Kämpe (University of Uppsala) we tested 51-kDa Abs by IPA in 15 APS type 1 patients, and 10 (66%) were positive. There was no association between the 51-kDa protein autoantibodies and ICA or GAD_{65} Abs. Five patients were followed-up for a mean period of 8 yr. None developed IDDM. One patient positive for ICA/GAD/51-kDa Abs died at the age of 18 yr after 10 yr of follow-up from complications arising from kidney failure; he still had a normal glucose tolerance test. At autopsy, no immunohistological abnormalities of the pancreas were demonstrated. These studies show that IDDM is a rare event in these patients, probably because of the presence of nonspecific serological markers of pancreatic autoimmunity and the lack of genetic markers of susceptibility to the disease.

Autoimmune thyroid diseases: The first description of autoimmune thyroiditis in APS type 1 dates back to 1964 (57). Subsequently, autoimmune destructive thyroid diseases (Hashimoto's thyroiditis or primary myxoedema), but not Graves' disease, were described in 2–13% of the cases. Primary myxoedema usually presented at an earlier age (mean, 9.5 yr) than Hashimoto's thyroiditis (mean, 17 yr) (4, 6, 15).

Four patients of our series (10%) developed Hashimoto's thyroiditis at a mean age of 20 yr; all were positive for thyroid microsomal autoantibodies, and 2 were also positive for thyroglobulin autoantibodies. Thyroid autoantibodies, in the absence of clinical thyroid disorders, were found in 10 of 37 (27%) of the remaining patients, all of whom maintained normal thyroid function during follow-up.

Lymphocytic hypophysitis or pituitary defects: Single or multiple pituitary defects have occasionally been described in APS type 1, first in 1971 (58, 59). In the large series of Ahonen, only one case of secondary hypogonadism has been described (6). In the absence of symptoms or signs of hypopituitarism, antibodies to PRL-secreting cells were demonstrated in patients with APS type 1 (60). It was reported that an autoimmune pituitary disease, defined as lymphocytic hypophysitis, can induce singular or multiple hormonal defects, but in this disorder, pituitary autoantibodies are very rare (61). Lymphocytic hypophysitis can be associated with other autoimmune diseases, mainly thyroiditis, but this disorder has never been described in patients with APS type 1 (61).

In our series of APS type 1 patients, we found three cases (7%) with evidence of pituitary hormonal defects (two with isolated defect of GH production and another with idiopathic diabetes insipidus), but morphological studies of the pituitary were not performed. None of these three patients had pituitary autoantibodies. PRL-secreting cell autoantibodies were demonstrated in three of six patients without PRL deficiency.

Autoimmune and immune-mediated gastrointestinal diseases.

Pernicious anemia: Pernicious anemia was first described in APS type 1 in 1955 (62). Subsequently, it was found in 11–13% of patients, most of whom were positive for parietal cell (PCA) and intrinsic factor autoantibodies (IFA) (4, 47, 63). In patients with IFA without pernicious anemia, a B_{12} absorption test revealed latent pernicious anemia in 38–66% of patients with IDDM (6, 64).

Three (7%) of our patients had pernicious anemia, which occurred at a mean age of 19.5 yr; 2 of these patients were positive for PCA and IFA. IFA were also found in 8 of 25 (32%) APS type 1 patients in our series without pernicious anemia. The disease developed in 3 of them at a mean age of 22 yr after a mean follow-up period of 7 yr. Pernicious anemia affected in total 15% of our patients.

Chronic atrophic gastritis: Chronic atrophic gastritis was first described in APS type 1 in 1962 (13). This disorder was present in 13–15% of the cases, most of whom were positive for PCA (4, 5). PCA can also be found in the absence of clinical disease (27).

PCA measured by immunofluorescence were found in 8 of 34 (24%) of our patients without pernicious anemia. In the majority of these patients, endoscopy demonstrated chronic atrophic gastritis type A with or without microcytic anemia.

Malabsorption: Malabsorption and/or steatorrhea have been described in patients with APS type 1 since 1953 (63, 65), with a prevalence of 18–22% (5, 6). Malabsorption can be due to a variety of causes, one of which is coeliac disease, as reported since 1955 (66). Other causes include cystic fibrosis (67), pancreatic insufficiency (10, 68), intestinal infections (*Giardia lamblia*, and *Candida*) (10), and intestinal lymphangectasia (69). In some of the cases of coeliac disease, reticulin autoantibodies were detected (7).

In our series, malabsorption was observed in six patients (15%), two of whom had coeliac disease.

Chronic active hepatitis. The initial observation of liver disease associated with APS type 1 was based on autopsy findings

of isolated case reports (3, 66). Subsequently, chronic hepatitis has been described in 8–26% of the cases (5, 6, 15). The age of clinical presentation was 5–21 yr, and the clinical course could vary from asymptomatic to fulminant, with a fatal outcome if not early treated (6, 70). Many cases presented the serological markers of autoimmune liver disease, such as autoantibodies to liver-kidney microsomes (LKM-Abs) and smooth muscle or mitochondria autoantibodies, but no (without) markers of viral hepatitis were detectable (70). The histological changes were consistent with a severe chronic active hepatitis (70). This form of autoimmune hepatitis benefited from immunosuppressive therapy associated with corticosteroids (70). Recently, it has been reported that sera from patients with autoimmune hepatitis and APS type 1 recognize the hepatic cytochrome P450IA2 (71).

Eight of our patients (20%) had chronic active hepatitis, (6 had LKM-Abs, 1 was negative, and 1 was not tested). One patient died of fulminant hepatic failure. Furthermore, LKM-Abs were present in 6 of 24 cases (25%) who did not have increased levels of hepatic enzymes. Two patients, 1 positive and 1 negative for LKM-Abs, revealed a transient increased level of hepatic enzymes during follow-up. This observation emphasizes the importance of the periodical determination of liver enzymes and LKM-Abs in subjects with APS type 1, because early diagnosis and immunointervention may prevent death or complications due to liver failure (6).

Skin autoimmune diseases.

Vitiligo: Vitiligo in APS type 1 was described for the first time in 1959 (67); subsequently, it was reported in 8–13% of cases (4–6). Vitiligo can appear from the first month after birth up to 15 yr of age (4, 5, 15). In APS type 1, vitiligo is associated with the presence of complement-fixing melanocyte autoantibodies (9, 72, 73). This marker has never been demonstrated in isolated vitiligo or that associated with other autoimmune endocrine diseases (73).

In our series, vitiligo was demonstrated in 5 patients. Complement-fixing melanocyte autoantibodies were demonstrated in all 5 cases as well as in 5 of 20 (25%) patients without vitiligo; of these, 1 developed vitiligo after 10 yr of follow-up (74). Therefore, vitiligo was demonstrated, in total, in 6 of 41 (15%) of our patients.

Alopecia: Association of alopecia with APS type 1 was reported for the first time in 1946 (2). The frequency of this disorder varies from 29–32% of all cases and involves scalp, eyelashes, eyebrows, axilla, and pubis (75). Alopecia appears from 3–30 yr of age (4–6, 15).

In our series, alopecia of various degrees was observed in 15 of 41 (37%) of patients.

Ectodermal dystrophy. Ectodermal dystrophy involves the nails and tooth enamel and consists of a defective dental enamel formation that was initially attributed to hypocalcemia. Currently, it is thought to represent a separate, possibly autoimmune, lesion, as it may also develop after correction of the calcium balance and was never seen in postsurgical hypoparathyroidism (20). Enamel hypoplasia was described in 77–82% of APS type 1 patients (6, 76). No delayed maturation, resorption, or root hypoplasia was observed. Dystrophy of the nails was also reported (77). Three of our patients were affected by dystrophy of the nails.

Keratoconjunctivitis. The first case of APS type 1 associated with keratoconjunctivitis was described in 1943 (78). This disorder was subsequently reported in 8–41% of APS type 1 patients (6, 13, 79). It was diagnosed on the basis of findings of irregular, initially slightly raised, confluent, and grayish corneal opacities; mild bulbar injection of the conjunctiva; and subsequent superficial corneal neovascularization of the hazy areas. It was not associated with hypoparathyroidism. We found keratoconjunctivitis in 5 of 41 (12%) of our patients.

Immunological defects

Cellular and humoral defects: Generalized cutaneous anergy has been described in three patients with chronic mucocutaneous candidiasis (21). The cutaneous anergy seemed to result from a deficiency of mediator production, probably migration inhibitory factor, or the presence of an inhibitor to this factor or to other mediators. Selective IgA deficiency and hypergammaglobulinemia were found in a family with APS type 1 (23). IgA deficiency in APS type 1 patients has been recently confirmed (69).

Asplenia. Asplenia is an uncommon finding and may be congenital (Ivemark's syndrome) or acquired. Acquired asplenia seems to be due to a progressive autoimmune-mediated destruction or vascular insult involving the spleen (80). This disorder was described for the first time in a patient with APS type 1 in 1968 (47). Its prevalence in this syndrome is still not clearly defined; it was demonstrated in 2 of 3 sisters (81) and in 4 of 9 other patients (80), but in none of 69 cases in a larger study (6). There were no consistent changes in T cell, B cell, or natural killer cell populations in the group of APS type 1 patients with or without asplenism (80). This disorder can be suspected on the basis of a peripheral blood smear that shows Howell-Jolly bodies, thrombocytosis, anysocites, poikylocytes, target cells, and burr cells (80). We found asplenia in 1 of 9 (11%) patients evaluated by computerized tomography or echography.

Cholelithiasis. Cholelithiasis was first reported in 1991 in four of nine patients with APS type 1 at an earlier age than that observed in the general population. It was hypothesized that it may be secondary to malabsorption, which causes disruption of the bile acid cycle; the subsequent low bile acid concentration in the gallbladder leads to precipitation of the cholesterol-bile stone (80). We did not find any case of cholelithiasis in nine patients evaluated by echography.

Other clinical manifestations. Calcifications of the basal ganglia were found in 17–30% of patients with APS type 1 (13). Calcified plaques of the tympanic membranes in patients with no history of ear infections were described in one third of the patients with APS type 1 (6); the same researchers found cutaneous vasculitis in two patients, squamous cell carcinoma of the oral mucosa in one, and rheumatoid arthritis in another.

Of 41 patients, we found endocranic calcification in 5 evaluated patients, Sjogren's syndrome in 5 (12%), cutaneous vasculitis with traces of cryoglobulinemia without markers of hepatitis virus B or C infection in 1 (2%), hemolytic anemia in 1 (2%), scleroderma in 1 (2%), carcinoma of the oral mucosa

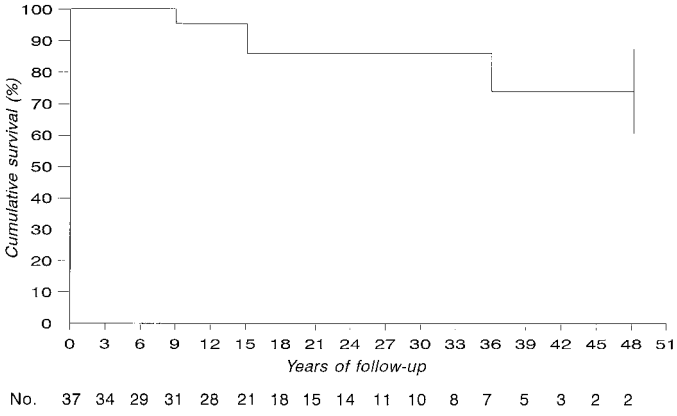

FIG. 2. Survival rate of the patients.

in 1 (2%), and adenocarcinoma of the stomach antrum in 1 (2%).

Survival

The survival of patients with APS type 1 before 1970 was very low; of 23 cases described during 1962, 16 died before the age of 30 yr (13). In recent series of studies, survival has increased; 9 of 68 (13%) patients from the Finnish group died: 1 of adrenal crisis, 1 of diabetic ketoacidosis, 2 of fulminant hepatic failure, 1 of carcinoma of the oral mucosa, 1 of accident, 1 of septicemia, 1 of sudden death related to hypoparathyroidism, and 1 of unknown causes (6).

Of 41 patients studied by us from 1967 to 1996, 4 (10%) patients died: 1 at the age of 11 yr of fulminant hepatic failure, 1 at the age of 16 yr of a generalized candidal infection due to immunosuppressive therapy for hemolytic anemia, 1 at the age of 18 yr for complications arising from kidney failure, and 1 at the age of 36 yr of carcinoma of the oral mucosa. The cumulative survival data are shown in Fig. 2.

Acknowledgments

We thank Dr. Jadviga Furmaniak (FIRS Laboratories, RSR, Cardiff, Wales) for testing 21-OH, 17α-OH, and P450scc autoantibodies and for the revision of the manuscript; Prof. Olle Kämpe (University of Uppsala) for testing antibodies to the 51-kDa antigen; Dr. Fabio Presotto, University of Padova, for the life table; and Mr. Beniamino Pedini, University of Padova, for the technical assistance.

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