Problem of asplenia in a patient with autoimmune polyglandular syndrome type 1

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Abstract

Autoimmune polyglandular syndrome (APS) type 1 is a rare autosomal recessive endocrinopathy characterized by the presence of two out of three major component diseases: chronic candidiasis, chronic hypoparathyroidism and autoimmune adrenal insufficiency. Other endocrine and nonendocrine conditions such as thyroid autoimmune disease, malabsorption or ectodermal dystrophy can be present. We report a case of a 15-year-old boy, who simultaneously presented chronic oral candidiasis, adrenal insufficiency and hypoparathyroidism. Additionally, the patient suffered from gastrointestinal involvement (malabsorption probably caused by secretory failure of exocrine pancreas) and asplenia.

At the age of 14 he developed leucoplakia lesions. The boy was properly treated for endocrine diseases as well as asplenia and chronic candidiasis.

Asplenia occurs very rarely in APS type 1, however for asplenic patients the risk of infection with encapsulated bacteria is higher so they require special treatment to prevent it.

Key words: *asplenia, autoimmune polyglandular syndrome, autoimmunity.*

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Introduction

Autoimmune polyglandular syndrome (APS) type 1, also known as APECED (autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy), is a very rare disorder, characterized by the failure of several endocrine glands as well as nonendocrine organs, caused by an immune-mediated destruction of endocrine tissues [1]. Despite its rarity, it shows segregation in some populations, where the prevalence is rather high: Finns 1 : 25,000 [2], Iranian Jews 1 : 9,000 [3], Sardinians 1 : 14,500 [4]. The common estimated incidence in the world is less than 1 in 100,000 per year [1, 5]. This autoimmune disease is caused by mutations in a novel gene featuring two PHD-type (plant homeodomain type) zinc finger domains (autoimmune regulator gene called *AIRE*), and is mapped to chromosome 21q22.3 [2, 6]. It is inherited in monogenic autosomal-recessive mode [7]. Many different mutations have been described in the *AIRE* gene [8], however the mutation R257X in exon 6 is one of the most frequent one causing APS type 1 [9].

To define APS type 1, at least two out of the three major component diseases: chronic mucocutaneous candidiasis, chronic hypoparathyroidism and autoimmune adrenal insufficiency, need to be present [10, 11]. The spectrum of associated minor clinical diseases include other autoimmune endocrinopathies (hypergonadotropic hypogonadism, insulin-dependent diabetes mellitus, thyroid autoimmune disease and pituary defects), autoimmune or immuno-mediated gastrointestinal disease (chronic atrophic gastritis, pernicous anemia and malabsorption), liver disease (chronic active hepatitis, cholelithiasis), autoimmune skin diseases (vitiligo and alopecia), autoimmune exocrinopathies (Sjögren's syndrome), rheumatic diseases, ectodermal dystro-

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phy (keratoconjunctivitis, nail dystrophy, defective dental enamel formation, faultless teeth), immunologic defects (T cell defect to *Candida albicans*, IgA deficiency, polyclonal hypergammaglobulinemia), acquired asplenia, neoplasias (epithelial carcinoma of the oral mucosa and of the esophagus, adenocarcinoma of the stomach), vasculitis, calcifications of basal ganglia and tympanic membranes [7, 8, 11]. In the majority of cases, the syndrome occurs in childhood, although further associated diseases (minor components) may not evolve until the fifth decade or later [12].

We report the case of a 15-year-old boy suffering from genetically confirmed APS type 1 with accompanying asplenia diagnosed after a close consultation with an immunologist, after which special treatment was introduced. This case also highlights the need for aggressive therapy of oral candidiasis to prevent development of epithelial carcinoma.

Case report

A 15-year-old boy with APS type1 was referred to Immunologic Ward because of recurrent upper and lower respiratory tract infections for the previous three years. His past history revealed that he was born to healthy parents with no history of immunologic or endocrine diseases. There were no complications either during pregnancy or at birth. He weighed 3900 grams at birth; Apgar score 10 points. His prenatal and postnatal course was unremarkable. He was not breast-fed, instead different kinds of formulas were given up to 20th month of age. At the age of 4 months vomiting followed by diarrhea appeared and from this period he progressively began to lose weight. At the age of four he was referred to hospital with stomach pain, protracted steatorhea and malabsorption with failure to thrive.

The concentration of chlorine in sweat was elevated in two tests (1st score 85.9; 2nd score 73.8). The boy's *CFTR* gene was tested to find final mutation, however, among the ten tested mutations only one allele of that gene was mutated, so CF can be neither confirmed nor excluded. Despite the lack of final genetic confirmation, abdominal form of cystic fibrosis (CF) was recognized and pancreatic enzymes were prescribed.

After three years, the boy was again admitted to hospital because of fever, pain of lower limbs' muscles and joints and skin rash. After performing blood tests (high leukocytes, elevated IgG level and ASO concentration, anti-tissues antibodies undetectable) the beginning of autoimmune connective tissue disease or Wissler-Fanconi syndrome was suspected.

At that time he started regular follow-up visits to a gastrologist in our hospital. His weight (18 000 grams) and height (111 cm) were beyond 3rd pc, he still complained of a loss of appetite and protracted steatorhea. His stool showed elevated fat balance (43.8 g/24 h) and the presence of candida. Appropriate treatment included special CF diet with nutritional formulas, pancretic enzymes (7500 U/kg), fat-soluble-vitamin supplementation and anti-candidal therapy (Nystatin). In routinely performed USGs, asplenia as well as mild cholelithiasis were discovered at the age of 9 and 11 respectively. In spite of complex treatment of gastrointerstinal problems, the height (130 cm) and weight (23 500 grams) were still beyond 3rd pc and there were episodes of stomach pain, diarrhea and oral candidiasis.

Before his 12th birthday, the boy lost 2500 grams of weight in 3 months, complained of weakness, total loss of appetite, malaise, apathy; some episodes of mild paresthesias and tetany of upper limbs were also reported. On physical examination there were hiperpigmented areas of knees, elbows and palms, signs of Chvostek (+) and Trousseau (+/–). Adrenal insufficiency was suspected and blood tests revealed ACTH > 2100 pg/ml, cortisol < 0.2 μg%, no hyponatremia or hyperkalemia, anti-tissues and antinuclear antibodies in indirect immunfluorescency test. A 24-hour urine collection aimed at detecting steroids confirmed adrenal insufficiency as there were no aldosterone's metabolites and a minimum amount of cortisol's and androgens' metabolites. Concomitantly a very low calcium (1.8 mmol/l) and slightly decreased level of parathormon (9.7 pg/ml) were detected with a normal range of pho sphates (1.6 mmol/l) concentration, which led to diagnosing hypoparathyroidism. Again, appropriate treatment with steroids (25 mg of hydrocortisone in 3 doses), calcium, magnesium and vitamin D_3 supplementation was administered. Three months later, the follow-up visit in Endocrinology and Metabolism Outpatient Clinic revealed satisfactory control of adrenal insufficiency and hypoparathyroidism; the boy felt stronger, less sleepy and his complexion was much fairer, he also put on weight of about 3500 grams. Because of exacerbation of oral candidiasis, gastroscopy was performed and candidasis of gastrointestinal tract was found. The treatment included prolonged anti-candidal therapy with Ketokonazole. The boy's DNA was analyzed for polyglandular autoimmune syndrome type 1 and the R257X mutation in *AIRE* gene was discoverd. The test was performed in the Department of Genetic Medicine of the Warsaw Medical University under supervision of Prof. Rafał Płoski. In the next three years, recurrent pharyngitis, laryngitis and bronchitis with productive cough appeared. The consulting pulmonologist performed spirometry (decreased maximal expiratory flow rate) and ordered Pulmozyme in regular nebulisations and vaccination against *Haemophilus influenzae* type b. As the boy still suffered from recurrent respiratory tract infections at the age of 14, he was referred to Immunology Unit. On physical examination we noticed white patches in his mouth unconnected with candida. After stomatologist consultation they were found to be diffuse lesions of leucoplakia. We also performed an accurate USG and scintigraphy test to make sure of asplenia in this patient which seemed to be a significant matter. Evaluation of humoral parameters revealed mild hipergammaglobulinaemia (IgG 1954 mg/dl), no response after three-time-

vaccination against HBV (anty HBs 0.0 mU/mL), significant level of autoantibodies to liver-kidney microsomes (LKM-Abs) in dilution up to 1 : 640. A slightly decreased level of C3 and C4 complement as well as zinc concentration were also found. No impairment in lymphocyte subpopulations and proper limphoproliferative response was discovered, although the elevated level of anti-candidal antibodies (1 : 320) required treatment. Because of asplenia the patient was inoculated with additional vaccines against capsulated bacteria i.e. *Streptococcus pneumoniae*, *Neisseria meningitidis* and against influenza virus. Tables 1 and 2 present the results of the latest immunological tests and antibody titers before and after Prevenar vaccination.

Due to mucocutaneous candidiasis, the prophylaxis with Itraconzole was incorporated. On the last follow-up visit the patient was in good condition, without any clinical and laboratory signs of candidiasis (anti-canidal antibodies 1 : 40), with normal liver enzymes.

Discussion

Autoimmune polyglandular syndrome type 1 is the first autoimmune disease that has been shown to be caused by the mutation of a single gene (*AIRE* for autoimmune regulator) [13]. It often appears early in life, typically in infants with persistent candidal infection of the skin and mucous

Table 1. Latest results of immunological blood tests

Parameter	Result		Norm range	
Humoral immunity				
IgA	2.39 g/l		0.66-3.70	
IgM	1.71 g/l		0.52-3.51	
IgG	**17.00 g/l**		6.63-15.87	
IgG1	11.05 g/l		4.35-11.20	
IgG2	3.38 g/l		1.16-7.02	
IgG3	3.70 g/l		0.23-1.57	
IgG4	**2.20 g/l**		0.19-1.13	
Complement system				
C3	80 mg/dl		90-180	
C4	13 mg/dl		10-40	
Cellular immunity				
CD3	1900 cells/µl	67%	800-3500	52-78
CD4	720 cells/µl	37.9%	400-2100	25-48
CD8	511 cells/µl	26.9%	200-1200	9-35
CD19	502 cells/µl	26.4%	200-600	8-24
NK	114 cells/µl	6%	70-1200	6-27
Lymphocyte blastic transformation test				
Control	PHA	IS PHA	CD3	IS CD3
468 ±180	7245 ±1514	15.5	7003 ±363	15

Table 2. Antibody titres before and after Prevenar vaccination

Serotype	4	6B	9V	14	18C	19F	23
before	1.015	0.097	0.760	2.305	0.692	4.059	0.183
after	28.285	1.190	4.104	84.256	5.530	4.917	1.712

The specific immunoglobulin G (IgG) antibody levels against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were measured by ELISA in the National Public Health Institute, Helsinki, Finland. Antibodies > 0.35 µg/dl were considered to be protective.

Table 3. Immunization against *Streptococcus pneumoniae* in asplenia or spleen dysfunction [32]

Age of examination	PCV13	PPV23	Reminding immunizations
2-6 mo	3 doses 4-8 weeks apart 1 dose at age 12-15 mo	1 dose at age 24 mo	1 dose PPV23 3-5 years after last dose of PPV
7-11 mo	2 doses 6-8 weeks apart 1 dose at age 12-15 mo	1 dose at age 24 mo	
12-23 mo	2 doses 6-8 weeks apart	1 dose at age 24 mo 8 weeks after last dose of PCV	
24-71 mo	2 doses 6-8 weeks apart	1 dose at age 24 mo 8 weeks after last dose of PCV	
6-18 years	1 dose PCV*	1 dose 8 weeks after PCV dose	
older then 18 years		1 dose 6-8 weeks after PCV dose	

**CDC. Recommended immunization schedules for persons aged 0 through 18 years — United States, 2011. MMWR 2011; 60. *CDC. Prevention of pneumococcal disease among infants and young children — use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010; 59 (No. RR-11). *CDC. Recommended adult immunization schedule — United States, 2011. MMWR 2011; 60. *CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; 46 (No. RR-8).*

membranes without the systemic infection generally associated with severe immunodeficiency. The diagnosis of APS type 1 is usually made later, when hypocalcemia due to hypoparathyroidism develops or adrenal insufficiency (Addison's disease) is recognized [14]. To define this syndrome, at least two of these diseases have to be present in one individual [12]. However, a recent publication by Italian researchers supported the idea of screening for AIRE mutations even in patients presenting only a single disease of APS type 1 spectrum [8].

From the immunologic point of view, considering complexity of APS type 1, we are especially interested in two issues: asplenism and chronic mucocutaneous candidiasis (CMC).

Chronic mucocutaneous candidasis generally occurs earliest in life and is thought to be the most frequent of the three major components of APS type 1. Chronic mucocutaneous candidasis affects the oral, vaginal and esophageal mucous membranes as well as the nails and dermis, it may also produce angular cheliosis. It is present in 73-100% of all patients [15] and is considered the clinical expression of an immunologic selective T cell deficiency with inability to respond *in vivo* and *in vitro* to candidal antigens [1]. However, in general these patients have a normal B cell response of serum antibodies to candidal antigens, which most likely prevents them from developing systemic candidiasis [16]. For this reason APS type 1 is also classified as an acquired immunodeficiency [15, 16]. It should be stressed that chronic candidiasis may lead in some patients to the development of epithelial carcinoma of the oral mucosa [17, 18]. This is why any lesions that are suspicious should be biopsied and aggressive anti-candidal treatment ought to be introduced to prevent late, dangerous complications [19]. Treatment of CMC has changed over the years. In the past, Amphotericin B associated with transfer factor yielded the best results [20]. At present, periodical treatment with Itraconazole is useful, although this drug is more effective in patients with nail infections and does not seem effective in those with mucosal infections [21, 22].

In case of our patient, before the age of 12 there were recurrent episodes of quite mild oral candidiasis, although numerous colonies of candida were twice detected in stool. It was accompanied by stomach pain and diarrhea, however all those symptoms were attributed to abdominal form of cystic fibrosis. The boy was treated periodically with Nystatin and probiotics by a gastrologist. During hospitalization in Immunologic Ward, leukoplakia of oral mucosa was diagnosed. Leucoplacia's lesions are believed to be the precancerous state of epithelial carcinoma. Luckily, according to Perheentupa *et al*. (1999), cancer of mucosae usually develops in patients with long-standing disease [23]. The patient has received prophylaxis with Itraconazole under liver enzymes control, leukoplakia's lesions are also monitored with great care by stomatologists.

Chronic hypoparathyroidism is the first endocrine disease to occur in the course of APS type 1 [1, 24], usually after CMC and before Addison's disease. It has been reported in 73-90% of the cases. Adrenal insufficiency appears commonly

before the age of 15 yr, however after chronic hypoparathyroidism [4, 15]. It occurs in 60-100% of cases [4]. In the case of our patient chronic parathyroidism and adrenal insufficiency appeared nearly simultaneously. The symptoms were obvious and after performing proper blood tests confirming suspicion of these diseases, efficient treatment was administered. The appearance of those new symptoms enabled us to put forward a proper diagnosis of APS type 1.

As the gastrointestinal system may be involved, symptoms of diarrhea/constipation, malabsorption with failure to thrive might rarely be identified as the first symptoms of developing APS type 1. Their evaluation requires investigation for other autoimmune disorders. Malabsorption and/or steatorrhea have been described in patients with APS type 1 since 1953, with a prevalence of 18-22% [9]. Malabsorption appears due to a variety of reasons: coeliac disease, cystic fibrosis, exocrine pancreatic insufficiency, intestinal infections (*Giardia lamblia*, *Candida*), and intestinal lymphangiectasia [25]. Symptoms from gastrointestinal tract prevailed in our patient's course of illness. He has been treated for an abdominal form of cystic fibrosis, however without genetic confirmation or exclusion of this disease. Consequently, steatorrhea, stomach pains and malabsorption might simply be a secretory failure of exocrine pancreas, which belongs to the list of gastrointestinal involvement in APS type 1.

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 [6]. The first episode of establishing cholelithiasis in our patient was quite early (at the age of 4), and was probably connected with malabsorption.

Asplenia is an uncommon finding and may be congenital (Ivemark's syndrome) or acquired. Acquired asplenia seems to be due to a progressive autoimmune-madiated destruction or vascular insult involving the spleen [6, 26]. This is why its prevalence in this syndrome has not been clearly defined yet. This disorder was described for the first time in a patient with APS type 1 in 1968 [27], next descriptions in literature refer to 2 of 3 sisters [26], and 4 of 9 other patients [6, 9]. However there were no such cases in a larger study [25]. There were no consistent changes in T cell, B cell or natural cell population in the group of APS type 1 patients with or without asplenia [6, 26]. This disorder can be suspected on the basis of peripheral blood smear that shows Howell-Jolly bodies, thrombocytosis, anisocites, poikilocites, target cells and burr cells [6, 28]. It is well-known that the spleen mechanically clears especially encapsulated bacteria from the bloodstream, produces antibodies against polysaccharide antigens gathered in IgG2 subclass, enhances phagocytosis and some processes of cellular immunity.

Fulminant, a potentially life-threatening infection is a major well-known risk in asplenic patients [29]. The most common organism is *Streptococcus pneumoniae*, but other encapsulated organisms such as *Haemophilus influenzae* and *Neisseria meningitidis* have been reported as significant pathogens [30]. All patients should receive all standard childhood and adolescent immunizations at the recommended age. Most importantly, vaccinations against encapsulated organisms, including pneumococcal conjugate and/or polysaccharide, *Haemophilus influenzae* type b conjugate, meningococcal conjugate and/or polysaccharide vaccines and influenza vaccine, should be administered on the standard schedule [31]. Table 3 presents the schedule of immunization against *Streptococcus pneumoniae* in asplenic individuals.

Our patient did not receive any vaccinations against *Streptococcus pneumoniae* and *Neisseria meningitides* or antibiotic prophylaxis before admission to Immunologic Ward. Luckily, he had not suffered from serious infections, which could have endangered his life, despite the lack of proper treatment. The patient had been vaccinated against *Haemophilus influenzae* because of recurrent laryngitis at the age of 12 on recommendation of a pulmonologist.

Additional vaccinations including conjugated (Prevenar Wyeth) and polysaccharide pneumococcal vaccines (Pneumo 23 by Aventis Pasteur) and meningococcal conjugated vaccine (NeisVac-C by Baxter) were administered during the patient's stay in Immunologic Ward. The patient frequents regular follow-up visits in our Outpatient Clinic. Currently he is in a good condition, the recurrence of pulmonary infections has decreased.

After diagnosing APS type 1, affected patients require close monitoring by numerous specialists including an immunologist, to prevent dangerous infections resulting from asplenia as well as oral cancer.

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