Nothing to disclose

Autoimmune polyglandular syndrome type 1 in Russia: clinical experience in 112 patients

Elizaveta Orlova, Leila Sozaeva[1] , Maria Kareva[1], Ekaterina Zakharova[3] , Bergithe E. Oftedal, Lars Breivik[2] , Per M. Knappskog[2] , Eystein S. Husebye[2]

[1]Endocrinology Research Center, Institute of Paediatric Endocrinology, Moscow, Russia; [2]Department of Clinical Science, University of Bergen, Bergen, Norway; [3]Research Center for Medical Genetics, Laboratory of Metabolic Disorders, Moscow, Russia

Background: Autoimmune polyglandular syndrome type 1 (APS-1) is a rare disease associated with mutations in the autoimmune regulator (AIRE) gene and characterized by mucocutaneous candidiasis (CMC), hypoparathyroidism (HP) and primary adrenal insufficiency (AI). Two of these three components are required for diagnosis

Objective and hypotheses: To describe Russian patients in terms of clinical, genetic, and immunological parameters.

Method: We have recruited patients with at least one of the major clinical components of APS-1 from all over Russia. Eligible patients were phenotyped, *AIRE* sequenced, and typical autoantibodies assayed.

Results

Table 1. Prevalence of the disease components in 112 patients with APS-1

Component	Frequency % (N)	Female/male	Age of onset (years)
Hypoparathyroidism	78 (88)	56/32	7.0 [1.5 – 16.3]
Mucocutaneous candidiasis	75 (84)	47/37	4.8 [0.1 – 21.5]
Adrenal failure	66 (75)	39/36	9.9 [3.3 – 28.1]
Alopecia	31 (36)	14/22	10.5 [4.3 – 23.0]
Enamel dysplasia (hypoplasia)	28 (32)	20/30	15.6 [0-29.0]
Malabsorbtion/chronic diarrhoea or obstipation	25 (28)	20/9	11.1 [2.0 – 40.0]
Pernicious anaemia	8 (10)	3/7	11.4 [5.0-25.0]
Type 1 diabetes	9 (12)	5/7	12.1 [1.7 – 21.2]
Autoimmune hepatitis	12 (14)	9/5	4.2 [1.5 – 13.5]
Vitiligo and/or hair depigmentation	8 (9)	5/5	12.1 [6.3-19.1]
Hypothyroidism/hyperthyroidism	13 (15)	11/4	9.4 [1.5 – 16.5]
Primary ovarian failure**	48 **	15/0	15.1 [13 – 19.2]
Periodical fever with rash	3	1/2	-
Angular erythema	3	1/2	-
Pigmental retinitis	3.6 (4)	2/2	-
Metaphyseal dysplasia	3.6 (4)	2/2	-
Chronic blepharitis, dry eyes	3.6 (4)		-
Asplenism	2 (2)	2/0	-
Ptosis	8 (9)	5/4	6.9 [0-8.0]

**among female patients older than 15 years

Fig 1. Classical triad and dyad

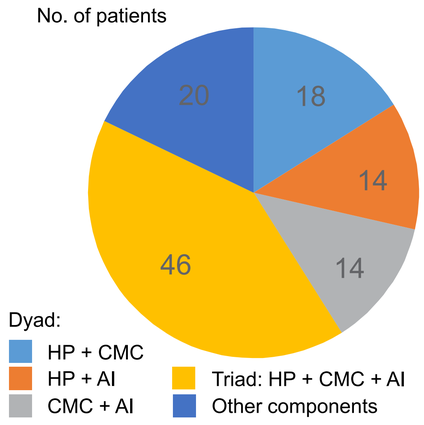

Table 2. Rare components

Component	N of cases
Methaphyseal dyplasia	4
Retinitis pigmentosa	4
PRCA*	1
Cerebellar ataxia	1
TSH-secreting adenoma	1

* PRCA - pure red cell aplasia

Table 3. Development of the clinical picture and AIRE mutations in APS-1 patients with one major component (16 patients)

Single major disease component	Age of manifestation (years)	Age at last examination (years)	Other components	AIRE mutation
CMC*	2	31	Alo (14)	R257X/R257X
CMC	3	36	Alo (13)	R257X/R257X
CMC	0.8	18	Alo (14)	R257X/NF
CMC	7	8	AH(5), FRA (5), ED (7)	R257X/ND
CMC	1.5	4	FRA (3), Mal (3)	R257X/R257X
CMC	0.3	2.5	AEr (1.5)	R257X/R257X
HP	8	12	*None*	R257X/R257X
HP	2.5	10	*None*	R257X/NF
HP	2.0	5	*None*	R257X/R257X
HP	8	8	*None*	R257X/R257X
HP	12	14	*None*	
HP	7	10	Mal (7)	R257X/R257X
HP	12.5	20	ED	R257X/R471C
HP	3	4	*None*	C302(C,Y)/NF
AI	12	15	D (3), B12 (5), V (9), ED , Pt (15), GINT (15)	p.Leu323sefs*51/NF
AI	5	8	*None*	ND

Alo alopecia, AH autoimmune hepatitis, Mal malabsorption, V vitiligo, Pt ptosis, GINT glucose intolerance, ED enamel dysplasia, AEr angular erythema, FRA fever with rash and arthralgia, * siblings

AIRE gene mutations (analyzed in 106 pts)

Arg257Stopp (R257X) mutation was the most frequent and was present in 74% of the alleles (63 pts were homozygouse, 27 pts were heterozygouse) and twenty different AIRE mutations were found, ten of them novel *(A58V; p.Leu 323serfs*51; A390P;821delG;A399P; del>500Stopp*; K221X;C302[C,Y];L13[P,L]; C434[*,C].*

Antibodies against INFs (investigated in 82 pts)

Abs against INFω	Positive	99%	N=1
Abs against INFα2	Positive	92%	N = 7

Case history (negative for Abs INFs)

- Male, 21 yrs old at last examination
- Hypoparathyroidism since 14 yrs of age
- Enamel hypoplasia
- R257X/R471C AIRE mutations

Conclusions: We have collected the largest cohort of patients with APS-1 published to date. Arg257Stopp AIRE mutation was the most frequent in Russian population. Ten novel AIRE mutations were found. Autoantibodies to INFω are useful for early diagnosis.

DOI: 10.3252/pso.eu.54espe.2015