Immunoglobulin G subtypes-1 and 2 (IgG1 and IgG2) can differentiate between autoimmune pancreatitis with associated cholangiopathy and primary sclerosing cholangitis

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IgG1 and IgG2 can distinguish patients with AIP-related cholangitis (IAC) from those with PSC

Background: Autoimmune pancreatitis (AIP) is a special form of chronic pancreatitis with a strong lymphocytic infiltration and two histopathological distinct subtypes, a lymphoplasmacytic sclerosing pancreatitis and idiopathic ductcentric pancreatitis.

IgG4 associated cholangiopathy (IAC) may be present at the time of AIP type 1 diagnosis or occurs later in the disease course.

IgG4 is considered reliable but not ideal marker for diagnosis of AIP type 1 with reported sensitivity between 71 to 81%.

It is essential to differentiate sclerosing cholangitis with AIP from primary sclerosing cholangitis (PSC) as the treatment and prognosis of the two diseases are totally different. It was aim of the study to find a marker for AIP IAC that would distinguish it from PSC.

Materials and method

Retrospective analysis of patients with AIP at our outpatient clinic at the Department of Digestive Diseases of Karolinska University Hospital in Stockholm, Sweden between January 2005 and october 2018.

Patients from the PSC registry from our department with proven histology were taken as a control group. The demographic, immunologic and clinical characteristics of both groups were recorded and analyzed.

The diagnosis of AIP was made according to the international consensus diagnostic criteria (ICDC) based on pancreatic histology, serology, imaging, other organs involvement and response to steroid therapy.

Blood samples for the measurement of all IgG subclasses were analyzed at the time of diagnosis before the patients received corticosteroid/immunosuppressive therapy.

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Results: 142 patients where all IgG subclasses were measured, 69 with AIP type 1and 73 with PSC. Patients with AIP and IAC had higher values in IgG2 when compared to AIP alone or PSC with a high specificity (97%) and high positive predicted value (91%). In patients with normal or low IgG2 or IgG4, a high IgG1 indicated PSC.

AIP versus PSC

Of all IgGs subclasses, only IgG2 (P<0.0001) and IgG4 (P<0.0001) distinguish patients with AIP from patients with PSC. The diagnostic performance of IgG2 and of the combination of IgG2 and IgG4 for the distinction of patients with PSC and AIP is further assessed by mean of sensitivity, specificity, positive predictive value, and negative predictive value. High IgG2 has a high specificity (97%) and positive predicted value (91%) to identify patients with AIP, but a low sensitivity (31%). The combination of high IgG2 and IgG4 retains similar specificity (93%) and positive predicted value (89%) but increases the sensitivity to 57%.

Distinction of PSC and AIP using IgG1, IgG2 and IgG4

We evaluated the diagnostic performance of IgG, IgG1 and IgG3 among patients with low or normal IgG2 and IgG4. In this subgroup, IgG1 was significantly higher in patients with PSC (mean±SD, 8.2±2.6 g/L) than in patients with AIP (6.7±2.2 g/L) (P=0.01), while no difference was observed for IgG3.

Furthermore, high IgG2 or IgG4 level were observed in 31% of the patients and identifies those with AIP (PPV=89%, 39/44); high IgG1 with low or normal IgG2 and IgG4 levels was observed in 27.5% of the patients and identifies those with PSC (PPV=85%, 33/39).

		PSC N (%)	AIP N (%)	P-value*	AIP without IAC N (%)	AIP with IAC N (%)	P-value*
ALL		73 (100)	69 (100)		14 (100)	55 (100)	
Sex							
	Males	51 (69.9)	38 (55.1)		4 (28.6)	34 (61.8)	
	Females	22 (30.1)	31 (44.9)	0.08	10 (71.4)	21 (38.2)	0.04
Age							
	<40	33 (45.2)	17 (24.6)		4 (28.6)	13 (23.6)	
	40-49	16 (21.9)	12 (17.4)		5 (35.7)	7 (12.7)	
	50-59	7 (9.6)	7 (10.1)		1 (7.1)	6 (10.9)	
	60-69	16 (21.9)	19 (27.5)		2 (14.3)	17 (30.9)	
	70+	1 (1.4)	14 (20.3)	0.001	2 (14.3)	12 (21.8)	0.33
IgG2							
	Mean±SD (g/L)	3.3±1.2	5.1±2.4	<0.0001	4.6±2.0	5.2±2.4	0.40
	Low (<1.15 g/L)	1	0		0	0	
	Normal (1.15-5.7 g/L)	70	46		11	35	
	High (>5.7 g/L)	2	21	<0.0001	3	18	0.52
	Sensitivity	21/67	31% (21-44)		18/53	34% (22-48)	
	Specificity	71/73	97% (90-100)		11/14	79% (49-95)	
	Positive predictive value	21/23	91% (72-99)		18/21	86% (64-97)	
	Negative predictive value	71/117	61% (51-70)		11/46	24% (14-38)	
IgG4							
	Mean±SD	0.4±0.4	2.0±3.9	0.002	1.2±1.2	2.2±4.3	0.15
	Low (<0.05 g/L)	8 (11.0)	0 (0.0)		0 (0.0)	0 (0.0)	
	Normal (0.05-1.25 g/L)	62 (84.9)	39 (56.5)		9 (64.3)	30 (54.5)	
	High (>1.25 g/L)	3 (4.1)	30 (43.5)	<0.0001	5 (35.7)	25 (45.5)	0.56
IgG2 and IgG4							
	Low or normal IgG2 and IgG4	68	30		8	22	
	High IgG2 or high IgG4	5	39†	<0.0001	6	33	0.37
	Sensitivity	39/69	57% (44-68)		33/55	60% (46-73)	
	Specificity	68/73	93% (85-98)		8/14	57% (29-82)	
	Positive predictive value	39/44	89% (75-96)		33/39	85% (69-94)	
	Negative predictive value	68/98	69% (59-78)		8/30	27% (12-46)	

Primary Sclerosing Cholangitis (PSC); Autoimmune Pancreatitis (AIP); Immune-associated cholangitis (IAC); Standard deviation (SD)
*P-values calculated with the Student t-test for continuous variables and the Fisher exact test for categorical variables
95% confidence intervals for the sensitivity, specificity, positive predictive value and negative predictive value calculated using the Binomial (Clopper-Pearson) exact method.
† 18 patients had normal IgG2 and High IgG4, 9 patients had High IgG2 and normal IgG4, 12 patients had High IgG2 and High IgG4
No difference in the distribution of IgG IgG1 and IgG3 between groups were found (See supplementary table 1).