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Evaluation of the Prevalence and Clinical Significance of elevated IgG Levels in Pediatric Liver Transplant Recipients

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Introduction

Within the past years, development of *de novo* autoimmune hepatitis (AIH) after orthotopic liver transplantation (OLT) has increasingly been regarded as an important cause for chronic graft dysfunction. *De novo* AIH is characterized by elevated IgG levels and liver specific autoantibodies. Typical histological signs are interface hepatitis, bridging fibrosis and liver cell necrosis (1). Elevated IgG levels may also occur for further reasons than *de novo* AIH such as other chronic inflammatory diseases or liver cirrhosis. Hypergammaglobulinemia (HGG) / elevated IgG levels are thought to be a marker for histologically advanced forms of fibrosis (2). It has been suggested that HGG in patients with severe chronic liver disease is due to the diminished removal of immunoglobulins by the liver (3). Moreover elevated IgG levels are an important diagnostic marker for *de novo* AIH. Therefore, we investigated the prevalence and clinical significance of IgG elevation in pediatric liver transplant recipients.

Patients and Method

Within 115 pediatric liver transplant recipients (0-17 years of age) regularly seen in our out patient clinic in June 2011, laboratory results collected during the last routine controls were screened for elevated serum IgG levels. In patients with IgG levels above the upper limit of normal, we retrospectively analysed demographic, laboratory (transaminases, autoantibodies) and histological features (interface hepatits, fibrosis) in search for signs of autoimmune/alloimmune hepatitis.

Conclusion

The prevalence of elevated IgG levels in our patients was 17.7% (20/115 patients), almost 3 time higher than the number of patients which were diagnosed as *de novo* AIH. Therefore, further reasons for elevated IgG levels should be considered and – if possible – ruled out. In cases of suspected early presentation of *de novo* AIH with elevated transaminases and positive liver specific autoantibodies but without typical histological features, pre-emptive treatment should be considered.

Results

Increased IgG levels were detected in 20 pediatric liver transplant recipients (11 m, 9 f, median 9 years). Average time after OLT was 7 years. Reason for OLT was biliary atresia in 13 patients, Wilson's disease in 2 patients and primary sclerosing cholangitis, acute liver failure, Caroli's disease, α-1 antitrypsin deficiency and biliary cirrhosis of unknown origin in one patient respectively. The maximal increase of IgG was 1,1-2,4 fold the upper limit of normal in this age group. Positive autoantibodies were found in the majority of the patients (10 SMA, 8 ANA, 3 SLA, 3 LKM-1). Fibrosis I-III° was present in 15 patients, liver cirrhosis in 4 patients. In 7 patients *de novo* AIH was diagnosed as autoimmune hepatitis and treated with steroids +/-azathioprine which showed a clinical response. All patients with LKM-1 autoantibodies (3/3 patients) were diagnosed as *de novo* AIH. An overview about the individual patients is shown in table 1. In figure 1, IgG levels of one patient (patient 6) are shown together with the appearance of autoantibodies and interface hepatitis. Interestingly, typical histological signs were absent in the first place but developed over time. Treatment with steroids and azathioprine lead to incomplete clinical and laboratory remission.

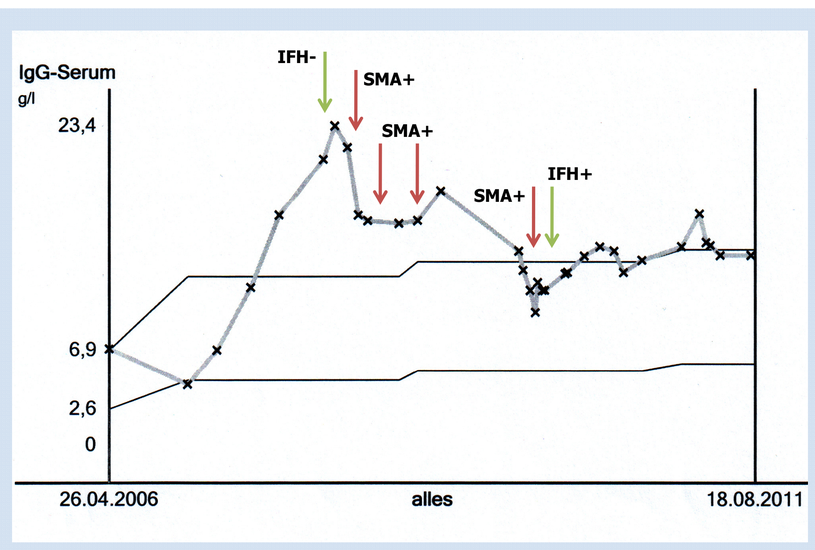

Figure 1: **IgG levels of patient 6 over a period of 5 years (IFH = interface hepatitis)**

Patient No.	gender	age (yrs)	date of OLT	initial organ disease	elevated IgG level	autoantibodies	histological signs	de novo AIH
1	male	15	1996	biliary atresia	~1,1-fold	SMA	fibrosis +, IFH -	no
2	female	15	2008	primary sclerosing cholangitis	~1,8-fold	negative	cirrhosis +, IFH -	unclear
3	male	12	2011	biliary atresia	~1,4-fold	negative	cirrhosis +, IFH -	unclear
4	male	7	2004	biliary atresia	~1,6-fold	SMA	fibrosis +, IFH -	unclear
5	female	8	2003	biliary atresia	~1,2-fold	ANA, SLA	cirrhosis +, IFH -	unclear
6	male	5	2006	biliary atresia	~1,9-fold	SMA	fibrosis +, IFH +	yes
7	female	1	2010	acute liver failure	~1,1-fold	LKM, SLA	fibrosis +, IFH +	yes
8	male	15	1999	biliary cirrhosis	~1,2-fold	ANA, SMA	fibrosis +, IFH -	no
9	female	4	2009	Caroli´s disease	~ 1,4-fold	ANA,SMA	fibrosis +, IFH +	yes
10	female	6	2005	biliary atresia	~1,4-fold	ANA,SMA	fibrosis +, IFH -	no
11	male	2	2010	biliary atresia	~1,4-fold	SMA, ANCA	fibrosis +, IFH -	unclear
12	female	9	2003	α-1 antitrypsin deficiency	~1,9-fold	ANA,LKM,SMA	fibrosis +, IFH +	yes
13	female	13	1998	biliary atresia	~1,2-fold	ANA,SLA	fibrosis +, IFH -	no
14	male	16	2007	Wilson´s disease	~1,7-fold	ANA, LKM, SMA	fibrosis +, IFH +	yes
15	male	9	2002	biliary atresia	~1,1-fold	negative	fibrosis +, IFH -	no
16	male	9	2002	biliary atresia	~1,1-fold	negative	fibrosis +, IFH -	no
17	male	13	2009	Wilson´s disease	~1,7-fold	ANA	fibrosis +, IFH +	yes
18	female	6	2006	biliary atresia	~2,4-fold	SMA	fibrosis +, IFH +	yes
19	male	9	2004	biliary atresia	~1,3-fold	negative	cirrhosis +, IFH -	no
20	female	13	1998	biliary atresia	~1,2-fold	SMA	fibrosis -, IFH -	no

Table 1: **Demographic, laboratory and histological features of the 20 patients with elevated IgG levels. Abb.: OLT, orthotopic liver transplantation; IFH, interface hepatitis**

References:

(1) Mieli-Vergani et al. (2008): Autoimmune paediatric liver disease. *World J. Gastroenterol.* 21, 3360-3367.

(2) Maruyama et al. (2007): Serum immunoglobulins in patients with chronic hepatitis C: a surrogate marker of disease severity and treatment outcome. *Hepatogastroenterology* 74, 493-498.

(3) Tanaka et al. (2007): Significance of hyperglobulinemia severe chronic liver diseases--with special reference to the correlation between serum globulin/IgG level and ICG clearance. *Hepatogastroenterology* 80, 2301-2305.