

# Protein Tyrosine Phosphatase-Like Protein Ia2 Antibodies and Glutamic Acid Decarboxylase 65 Antibodies (GADA) are not Associated With Sarcoidosis

Papadopoulos I, Konstantinos, Sundkvist Göran, Borg Henrik, Hallengren Bengt

Department of Endocrinology, University of Lund, Malmö University Hospital, S-205 02 Malmö, Sweden

**T**he existence of an association between glutamic acid decarboxylase 65 antibodies (GADA) and/or IA2 antibodies and sarcoidosis was evaluated.

**Materials and Methods:** 78 patients with documented sarcoidosis, divided according to the presence (N=37) or absence (N=41) of autoimmune manifestations were evaluated for GADA and IA2 antibodies using a radioligand assay with human recombinant 35S-labeled GAD65 and IA2 respectively.

**Results:** Two patients with GADA (2.6%) and one (1.3%) with IA2ab, both in the group of patients with autoimmunity associated sarcoidosis were found. The GADA positive patient had manifest Type 1 diabetes that succeeded sarcoidosis. IA2 ab-positivity was seen among patients with isolated sarcoidosis. GADA and IA2ab frequencies were not increased compared to reference subjects (2-3%).

**Conclusions:** No clear association between sarcoidosis and GADA and/or IA2ab was found. In patients with sarcoidosis, GADA seem to be associated with type 1 diabetes or other autoimmune manifestations rather than with sarcoidosis per se.

**Key Words:** Sarcoidosis, Autoimmunity, Islet

**Correspondence:** Konstantinos I. Papadopoulos, Dept. of Endocrinology, Malmö University Hospital, S-205 02 Malmö, Sweden

**E-mail:** kostasp@truemail.co.th

cell antibodies, Glutamic acid decarboxylase, IA2

Received: 20/05/2005- Accepted: 17/04/2006

## Introduction

Sarcoidosis is a systemic disease of unknown etiology, featuring noncaseating granulomas, predominantly in the lymph nodes, lungs, eyes and skin, although any organ may be involved, and by several immunological abnormalities.<sup>1</sup> We and others<sup>2-7</sup> have also reported of high frequency of endocrine and gastrointestinal autoimmunity in patients with sarcoidosis. The frequencies of Type 1 diabetes and the classical autoimmune marker islet cell antibodies (ICA) were not increased in patients with sarcoidosis.<sup>2</sup> ICA, are unspecific antibodies detected with immunofluorescence on human pancreas, and comprise two major components: antibodies against glutamic acid decarboxylase 65 (GADA) and antibodies against a protein tyrosine phosphatase IA2 (IA2 ab).<sup>8</sup> Recently two patients positive for IA2ab with sarcoidosis and Type 2 diabetes were reported and an association between IA2 and sarcoidosis was suggested.<sup>9</sup> The frequencies of both

GADA and IA2ab in sarcoidosis have however never been elucidated. The aim of this study was to examine whether there was an association between GADA and/or IA2ab and sarcoidosis in a well-characterized group of patients with sarcoidosis.<sup>2,3</sup>

## Patients and Methods

**Patients:** Between January 1980 and December 1991, seventy-eight patients with documented sarcoidosis attending the Department of Pulmonary Medicine, Malmö University Hospital were evaluated (34 females, 44 males, median age at the time of the study 48 years, range 22-81), serum samples were collected in 1991 and frozen in aliquots for later analyses.<sup>2,3</sup> The diagnosis of sarcoidosis was based on histological or clinical, biochemical and radiological evidence. The seventy-eight patients with sarcoidosis were divided into two subgroups according to the presence (N=37) or absence (N=41) of autoimmune manifestations (Autoimmune Addison's disease, thyroid autoimmunity, Type 1 diabetes, gluten immune reactivity and gastric autoimmunity).<sup>2,3</sup> Twenty-eight of the 78 patients (35.9%) had been treated with corticosteroids (median 42, range 2-240 months) and there was no difference in the length of treatment with corticosteroids between the subgroups of isolated sarcoidosis or sarcoidosis associated with autoimmune manifestations. Type 1 diabetes was diagnosed in patients (n=2) in need of exogenous insulin for avoiding ketoacidosis and maintaining adequate metabolic stability.<sup>2</sup> There was no time limit applied for the appearance of insulin requirement as Type 1 diabetes associated with autoimmune disorders may have a rather slow progression of the disease.<sup>2</sup> The study was approved by the Ethics Committee of the Medical Faculty, University of Lund.

**Glutamic acid decarboxylase antibodies (GADA):** GADA were measured by a radio-

ligand assay with human recombinant 35S-labeled GAD65. A GADA index >10.2 (>97.5% of 196 adult controls) was considered abnormal.<sup>8,11</sup>

**IA2 antibodies:** IA2 antibodies were also measured by a radioligand assay with human recombinant 35S-labeled IA2. An IA2 index value >1.1 (>97.5% of 196 adult controls) was considered abnormal.<sup>8,11</sup>

## Results

In 78 patients with sarcoidosis, only 2 had GADA (2.6%, one male, one female, table 1) and 1 (1.3%, one female) had IA2ab. Both GADA positive patients were found in the group of patients with sarcoidosis associated with autoimmune manifestations (n=37) and one had manifest Type 1 diabetes succeeding sarcoidosis, IA2 ab-positivity was seen in the group of patients with isolated sarcoidosis (n=41). The frequency of GADA and IA2ab was not increased compared with that (2-3%) of reference subjects. The associated autoimmune diseases seen in the GADA positive patients in each patient are shown in table 1.

## Discussion

In the present study we did not observe any association between GADA and/or IA2ab in patients with sarcoidosis. To the best of our knowledge the frequency of GADA has never been investigated in patients with sarcoidosis and only sporadic cases have been reported.<sup>9,10</sup> Of the 2 patients with GADA, however, one had Type 1 diabetes in the context of PGA syndromes (table 1). IA2ab was not seen in that patient, probably because of the long duration of the disease. As we reported in our previous work,<sup>2</sup> the frequency of Type 1 diabetes in sarcoidosis was not significantly raised compared to controls and ICA were negative in all patients.

**Table 1. Characteristics of 2 patients with sarcoidosis and associated GAD antibodies.**

Patient No/gender	Age (year)		GADA index (<10.2)	Associated entities (Age at onset)
	at study	at diagnosis of sarcoidosis		
1 M	67	61	17.7	AGA-IgA, no clinical coeliac disease
2 F	57	23	16.4	Type 1 diabetes (29), ATD (35), Coeliac disease (44), transiently positive adrenal anti-bodies [PGA type III]

M: male, F: female, GADA: Glutamic acid decarboxylase antibodies, ATD: autoimmune thyroid disease, AGA: antigliadin antibodies, PGA: polyglandular autoimmune syndrome.; Protein tyrosine phosphatase-like protein IA2 antibodies and Glutamic acid decarboxylase 65 antibodies (GADA) are not associated with sarcoidosis

IA2 was previously noted in 2 patients with Type 2 diabetes and sarcoidosis.<sup>9</sup> We studied 78 patients with sarcoidosis and found one patient with IA2ab but that patient lacked diabetes mellitus (her IA2ab titer was 2.0 with an IA2ab index of <1.1) and she did not have other autoimmune phenomena. Moreover, the frequency of IA2 was not significantly raised compared to controls. Hence, it is unlikely that there was any valid/definite association between sarcoidosis and IA2ab.

### Conclusion

In conclusion, this study found no clear association between sarcoidosis and GADA and/or IA2ab. If GADA and/or IA2ab are detected in patients with sarcoidosis, these antibodies are more likely to be associated with

type 1 diabetes or other autoimmune manifestations rather than sarcoidosis.

### Acknowledgements

Grants from the Albert Pahlsson foundation, the Child Diabetes fund, the Juvenile Diabetes foundation-Wallenberg Diabetes research Program (K98-99JD-128B), Lundström Foundation, Malmö Diabetes Association, Novo-Nordic Foundation, Research Funds Malmö University Hospital, Swedish Diabetes Association, Swedish Medical Research Council (7507 and 5913), and University Funds Lund University supported this study. We thank Ulrika Gustavsson and Christina Rosborn for their valuable technical assistance.

### References

1. Bell NH. Endocrine complications of sarcoidosis. *Endocrinol Metab Clin North Am* 1991; 20: 645-54.
2. Papadopoulos KI, Hornblad Y, Liljebladh H, Hallengren B. High frequency of endocrine autoimmunity in patients with sarcoidosis. *Eur J Endocrinol* 1996; 134: 331-6.
3. Papadopoulos KI, Sjöberg K, Lindgren S, Hallengren B. Evidence of gastrointestinal immune reactivity in patients with sarcoidosis. *J Intern Med* 1999; 245: 525-31.
4. Papadopoulos KI, Hallengren B. Polyglandular autoimmune syndrome type III associated with coeliac disease and sarcoidosis. *Postgrad Med J* 1993; 69: 72-5.
5. Papadopoulos KI, Hornblad Y, Hallengren B. The occurrence of polyglandular autoimmune syndrome type III associated with coeliac disease in

- patients with sarcoidosis. *J Intern Med* 1994; 236: 661-3.
6. Nakamura H, Genma R, Mikami T, Kitahara A, Natsume H, Andoh S, et al. High incidence of positive autoantibodies against thyroid peroxidase and thyroglobulin in patients with sarcoidosis. *Clin Endocrinol (Oxf)* 1997; 46: 467-72.
  7. Mc Cormick PA, Feighery C, Dolan C, O'Farrelly C, Kelliher P, Graeme-Cook F, et al. Altered gastrointestinal immune response in sarcoidosis. *Gut* 1988; 29: 1628-31.
  8. Borg H, Fernlund P, Sundkvist G. Protein tyrosine phosphatase-like protein IA2-antibodies plus glutamic acid decarboxylase 65 antibodies (GADA) indicates autoimmunity as frequently as islet cell antibodies assay in children with recently diagnosed diabetes mellitus. *Clin Chem* 1997; 43: 2358-63.
  9. Yamada K, Yuan X, Inada C, Hayashi H, Koyama K, Ichikawa F, et al. Combined measurements of GAD65 and ICA512 antibodies in acute onset and slowly progressive IDDM. *Diabetes Res Clin Pract* 1997; 35: 91-8.
  10. Takahashi T, Kazama Y, Shimizu H, Yoshimoto M, Tsujisaki M, Ishiguro A, et al. Association of idiopathic thrombocytopenic purpura and type 1 diabetes mellitus in a patient with sarcoidosis. *Nihon Rinsho Meneki Gakkai Kaishi* 2001; 24: 81-6.
  11. Borg H, Fernlund P, Sundkvist G. Measurement of antibodies against glutamic acid decarboxylase 65 (GADA): two new <sup>125</sup>I assays compared with [<sup>35</sup>S]GAD 65-ligand binding assay. *Clin Chem* 1997; 43: 779-85.