Reversible IgA deficiency in hypothyroidism

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Summary
A 50-year-old woman developed pronounced IgA-deficiency and hypothyroidism after 131I treatment for Graves’ disease. The deficiency state was associated with a severe sinobronchial syndrome. Treatment with L-thyroxine resulted in a normal IgA concentration and a dramatic clinical improvement. Of the various possible underlying mechanisms, impaired synthesis of IgA light and heavy light chains seemed most probable. Impaired production of J-chain was excluded.

Introduction
Isolated deficiency of IgA is by far the most commonly identified defect of the immune system in humans. The prevalence of this dysgamma-globulinaemia in a Swedish population has been estimated to 1/700 (Bachmann, 1965). The defect may appear in otherwise healthy persons or may be associated with an increased incidence of infections, particularly respiratory. An increased incidence in malabsorptive states and so-called autoimmune diseases including hepatitis has also been reported. The evolution of secondary IgA deficiency may occur as a part of generalized deficiency of immunoglobulins, as in multiple myeloma or protein-losing states. Secondary IgA deficiency has also been reported in connection with phenytoin treatment (Aarli and Tönder, 1975) and in patients with ulcerative colitis receiving sulphasalazine treatment (Savilathi and Pelkonen, 1979).

The purpose of this report is to present a case of isolated symptomatic IgA-deficiency occurring in a woman with hypothyroidism and responding to treatment of the endocrine disease.

Case report
The patient is a woman born in 1919. Her family history is unremarkable. When aged 43 years she had an episode of atrial fibrillation which was treated with quinidine sulphate, and developed an exanthema. At the age of 50 years, she had persistent atrial fibrillation, rapidly lost 12 kg in weight and had diarrhoea. A diagnosis of a florid Graves’ disease was confirmed by high serum values of protein-bound iodine (PBI), T₃ resin and radioactive iodine uptake. Treatment was given with 5 mCi of 131I and additional treatment was started with carbimazole 15 mg/hr. However, the patient developed a generalized exanthema of the morbilliform type and became febrile. A generalized lymphadenopathy and a slight splenomegaly were noted. Leucopenia (WBC=1×10³/l) and thrombocytopenia (platelets, 88×10⁹/l) were also present. L.E. cells were not found and rheumatoid factor was absent in serum samples. Serological reactions for listeriosis, mononucleosis, Mycoplasma pneumoniae and toxoplasmosis were all negative. The serum protein pattern was normal except for a selectively raised concentration of IgA to 3.6 g/l (Fig. 1). The other immunoglobulins were normal. Biopsy of an enlarged lymph gland demonstrated non-specific proliferation of reticulum cells. The thyrostatic drug was withdrawn and the thyrotoxic state was terminated by administration of Lugol’s solution and chlorpromazine.

In 1970, the patient was clinically and biochemically euthyroid but her atrial fibrillation persisted. Two attempts to convert to sinus rhythm by DC countershock were unsuccessful and the patient was given acetylcholinoxin 0.2 mg daily. The skin manifestations and lymphadenopathy disappeared, but the spleen remained slightly enlarged. Her blood picture was, however, normalized.

In 1972 the patient had a right-sided carpal tunnel syndrome which was treated surgically, and the first radioimmunoadsorption of TSH was performed with a normal result (Fig. 1).

In 1972 the patient was troubled by an increasing number of upper respiratory infections. At examination the spleen was slightly enlarged. The white blood count and serum protein analyses, including immunoglobulins were all normal. In 1975 hypothyroidism was clinically suspected but the TSH level was still normal. No TRH test was performed.

During the ensuing year the patient’s condition was dominated by respiratory infections. She had repeated episodes of sinusitis and/or bronchitis. In 1977 the spleen was no longer enlarged and bone
marrow biopsy, needle aspiration of the spleen and lymphography were performed but no malignant lymphoma was found. The number of plasma cells in the bone marrow was normal; indirect immunofluorescent staining for immunoglobulins showed 7% IgG reactive cells, 93% IgM and 1% IgA reactive cells as compared to an expected 15-20%. The concentration of IgA was subnormal (0.3 g/l) and that of TSH remained normal.

In 1978 she had 12 sinobronchial infections, one episode of pneumonia (confirmed by X-ray) and several episodes of conjunctivitis. The pneumonia was treated with doxycycline hydrochloride. This drug was also sporadically given for other respiratory tract infections. The patient received no long-term treatment with either antibiotics or sulphonamides. She also had 2 episodes of intestinal distress with diarrhea. The IgA concentration was now 0.005 g/l. A family investigation revealed normal IgA concentrations in 2 siblings, a husband and 3 children.

In 1979 the TSH concentration was elevated, at 46 U/l, and the patient was clinically hypothyroid. The IgA concentration was 0.006 g/l. All other serum proteins including immunoglobulins and complement factors (C3, C4) were normal. A separate analysis of IgA, IgM and J-chain (joining) in plasma and saliva was performed (Table 1) and J-chain production was judged to be normal. There was a pronounced but not total deficiency of IgA in plasma and saliva. IgM concentrations were normal. A complete blood count was normal as were the biopsies from small intestine and rectum. The number of plasma cells in these biopsies was normal but direct immunofluorescence for immunoglobulins in the rectal biopsy revealed a complete absence of IgA staining cells. Immunofluorescent staining of the small intestinal biopsy was unsuccessful. A 14C-cholyl-glycine breath test was abnormal with 0.5% and 0.96% 14CO2 expired after 3 resp 6 hours (normal <0.35 and 0.5%, respectively). The number of T-lymphocytes was normal as was their function as judged by phytohaemagglutinin and Con-A-stimulation. The granulocytes had normal phagocytic, bacterial killing and chemotactic abilities. Treatment commenced with L-thyroxine resulting in normalization of TSH concentration and a steadily increasing IgA level. At the latest analysis the level was 1.4 g/l, i.e. well within the normal range. Since the start of treatment the patient has had only 2 minor episodes of the typical common cold.

**Discussion**

An increased susceptibility towards respiratory infections in hypothyroidism has been noted by several authors (Bansi, 1955; de Groot and Stanbury, 1975). However, to the author's knowledge, this feature has not earlier been found to be associated with IgA-deficiency. Finnish authors (Kuitunen et al., 1971) have noted a high frequency of IgA-deficiency in children with thyroiditis but this has been shown to be a permanent and irreversible deficiency, probably inherited as an autosomal dominant trait. The unique feature of the present case in the evolution of an acquired, clinically significant and reversible IgA-deficiency associated

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**Table 1.** IgA, IgM and J-chain concentrations in plasma and saliva (Grubb, 1978). Reference range in parentheses

<table>
<thead>
<tr>
<th></th>
<th>IgA</th>
<th>IgM</th>
<th>J-chain (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>0.05</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>(0.5-3)</td>
<td>(0.4-2.0)</td>
<td>(0.6-2.6)</td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td>0.003</td>
<td>0.015</td>
<td>0.03</td>
</tr>
<tr>
<td>(0.05-0.3)</td>
<td>(&lt;0.009)</td>
<td>(0.15-0.95)</td>
<td></td>
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**Fig. 1.** Plasma IgA concentration (g/l) in relationship to thyroid function (TSH concentration) in the patient with surgically treated right-sided carpal tunnel syndrome.
with an iatrogenic (131I) hypothyroidism. As no TRH tests were performed the diagnosis was probably delayed. The carpal tunnel syndrome in 1972 might well have been an early manifestation of myxoedema. In any case, the patient's IgA concentration seems dependent upon her current thyroid status; high when toxic, subnormal when myxoedematous and later restored to normal on adequate substitutions (Fig. 1). There was no evidence of chronic thyroiditis in the patient, nor other autoimmune diseases, although the side effects of carbimazole and quinidine treatment were suggestive of systemic lupus erythematosus. Absence of L.E. cells, antinuclear factor and the subsequent course, however, exclude this possibility.

IgA-deficiency is not a common feature of hypothyroidism. On reviewing 7 patients with hypothyroidism where individual immunoglobulins had been analysed before and after therapy, no evidence of an association between plasma IgA concentration and thyroid function could be found. The patient's susceptibility to infections constituting a classic sinobronchial syndrome were clearly associated not only with sub-normal plasma IgA but also with sub-normal salivary levels (Table 1). Thus the patient probably had impaired immune defence in her respiratory tract. The abnormal 14C-cholylglycine breath test indicative of abnormal bacterial overgrowth in the proximal lumen may also be explained by the intestinal IgA deficiency. In this case there was no evidence of impaired lymphocyte or granulocyte function, which may be alternative mechanisms for decreased resistance against infections in hypothyroidism. The data shown in Table 1 together with the clinical course exclude the possibility that the thyroid function determined the production rate of the secretory component which joins 2 IgA molecules together and prevents proteolytic degradation of the dimers. The data given in Table 1 also seem to preclude the possibility of abnormal J-chain production in hypothyroidism. The plasma concentration of the joining chain is normal.

Three further possibilities remain. Antibodies against IgA might have been present either owing to or quite independent of the thyroid dysfunction. Experiments to test this possibility were not performed but it seems improbable that an antibody in vivo should block the specific antibody site used in the immunoassay of the protein in plasma. A drug-induced deficiency seems improbable with regard to the course (Fig. 1). Finally, the production of the IgA heavy and/or light chains might have been impaired by the hypothyroid state. This could be due to a decrease in IgA-secreting cells or blocked intracellular synthesis. A synthetic failure was substantiated by the lack of IgA-secreting cells demonstrated in both bone marrow and rectal biopsies. However, the apparent influence of the thyroid function on the IgA synthetic rate remains unexplainable.

Acknowledgment

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References


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