The Journal of Laryngology & Otology (2007), ***121***, *1204–1206.*

doi:10.1017/S002221510700014X
Printed in the United Kingdom
First published online 1 August 2007

Clinical Record

Common variable immunodeficiency syndrome: a difficult diagnostic problem

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Abstract

Objective: We present a rare case of an adult male with undiagnosed common variable immunodeficiency syndrome who presented to the ENT department with refractory chronic sinusitis and otitis media with effusion.

Method: Case report and a review of the international literature concerning common variable immunodeficiency syndrome in adults and upper respiratory tract involvement.

Results: A 37-year-old male presented to the ENT department with refractory chronic sinusitis and otitis media with effusion. The diagnosis of common variable immunodeficiency syndrome was delayed, and difficult, primarily due to minimal symptoms with no lower respiratory tract involvement and negative past or family medical history.

Conclusion: Early diagnosis helps to prevent morbidity and even mortality. This article highlights how difficult and important it is to make an early diagnosis of common variable immunodeficiency syndrome. Early diagnosis will only be made by increased awareness of this condition.

Key words: Adult; Rrefractory; Sinusitis; Otitis Media with Effusion; Common Variable Immunodeficiency

Introduction

Common variable immunodeficiency syndrome is characterised by diversity in its clinical presentation. Patients usually present with recurrent upper tract or lower tract respiratory infections. It is of great importance that doctors are aware of this condition, as the early onset of treatment can prevent any sequelae. We present one such case to highlight the importance of awareness of this condition amongst the medical specialities as an early diagnosis can prevent morbidity and mortality.

Case report

A 37-year-old male was referred to ENT with recurrent nasal obstruction, nasal discharge and right ear blockage of two years duration. There was nothing significant in his past medical history apart from an episode of pleurisy and pneumonia with haemoptysis in 1998.

ENT examination revealed a right otitis media with effusion, congested nasal mucosa and lymphoid hyperplasia in the post-nasal space. The patient was commenced on a topical nasal steroid spray but had three more episodes of acute sinusitis leading to a recurrence of his symptoms.

A computed tomography scan of his sinuses showed minor inflammatory changes. He subsequently underwent examination under anaesthesia of the post-nasal space and biopsy of lymphoid tissue with right grommet insertion. Final histology of the post-nasal biopsy revealed features consistent with adenoid tissue. He was well following the surgical intervention. However, 18 months later his symptoms recurred. ENT examination revealed mucopurulent nasal discharge and right otitis media with effusion, the grommet having been extruded. He was treated with oral doxycycline and nasal decongestants. Despite medical treatment, his symptoms persisted. He underwent functional endoscopic sinus surgery (right), submucous resection and re-insertion of right grommet. He remained symptomatic despite surgery. This posed a dilemma and a decision was made to assess his immune profile. Immunoglobulin level assay was arranged. The results of the immunoglobulin (IG) level assay showed IgG (0.4 mg/dl), IgA (0.1 mg/dl) and IgM (0.86 mg/dl). He was referred to a haematologist and further investigations showed B cell count of 12% with normal light chain expression and T cells with 43% CD4 positive and 24% CD8 positive. His erythrocyte sedimentation rate was 24 mm/h and C reactive protein 25 mg/l. Renal and liver function were normal. Serum iron was within the normal range but his transferrin saturation was mildly low of 12%. Beta-2-microglobulin was 2.3 mg/l (Table I). A further referral was made to an immunologist with a diagnosis of common variable immunodeficiency syndrome.

He was treated with replacement therapy with immunoglobulin. The patient developed diarrhoea six months after his first treatment and underwent biopsy of his bowel to rule out lymphoma. He is still undergoing treatment with immunoglobulin but his infections have been significantly reduced.

Discussion

Primary antibody deficiency is defined as a reduction or absence of one or more immunoglobulin isotypes or subclasses, when no other contributory disorder is present.

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Accepted for publication: 22 May 2007.

TABLE I

RESULTS OF ROUTINE LABORATORY TESTS

Variable (units)	Results	Normal range*
Haemoglobulin (g/dl)	14.5	12.7–16.7
White blood cell count (cu/mm^3)	8.8 $\times 10^3$	3×10^3–11×10^3
Lymphocytes (cu/mm^3)	2.6 $\times 10^3$	1300–3500
B cells (%)	12	40–60
CD4+ T cells (%)	43	27–61
CD8+ T cells (%)	24	14–46
Erythrocyte sedimentation rate (mm/h)	24	0–10
C-reactive protein (mg/L)	25	0–10
Serum iron (μmol/l)	9.7	9–30
Transferrin saturation (%)	12	20–50
Beta$_2$ microglobulin (mg/l)	2.3	≤2.7
IgG (mg/dl)	0.4	620–1400
IgA (mg/dl)	0.01	80–350
IgM (mg/dl)	0.86	45–250

*Normal range values according to Singleton's pathology department values

There are three major forms of antibody deficiencies namely:-

1 X-linked agammaglobulinaemia (XLA, Bruton's agammaglobulinaemia).
2 Common variable immunodeficiency (CVID) which includes IgG subclass and specific antibody deficiencies.
3 Selective immunoglobulin A (IgA) deficiency.

There are other rare antibody deficiency syndromes with similar features to those of the three major deficiencies.[1] Although the primary immunodeficiencies are rare, IgA deficiency has an estimated frequency of between 1 in 320 and 1 in 800,[2] and five per million have common variable immunodeficiency syndrome.[3]

Primary immunodeficiency syndromes, especially antibody deficiency, can present at any age. The incidence of common variable immunodeficiency syndrome has two peaks, one in the first five years of life with a second peak in the second decade. However, it should still be considered in elderly people.[4] Antibody deficiencies are the commonest primary immunodeficiency and are most likely to present with recurrent ENT infections.[5]

Fluctuating levels of different IgG subclasses as well as IgA and IgM suggest that diagnosis of common variable immunodeficiency may also be associated with functional and quantitative deficits of cellular immunity (CD4 and lymphopenia).

- **Sinusitis and otitis media with effusion can be the first presentation of common variable immunodeficiency syndrome in an adult**
- **Increased awareness of the condition will result in early diagnosis**
- **Early diagnosis will prevent morbidity and mortality**

Common variable immunodeficiency syndrome diagnosis includes a heterogeneous group of males and females who have in common the clinical manifestations of deficient production of all types of major immunoglobulin classes. Immunodeficiency should be suspected in patients with recurrent acute rhinosinusitis that cannot be attributed to another underlying cause (anatomic obstruction/underlying mucociliary defect), a persistent infection that does not respond to adequate antibiotic therapy, infections at other sites (especially pneumonia, sepsis and meningitis), unusual sinus pathogens or severe infections, or a family history of immunodeficiency.[6]

An audit in the United Kingdom showed that the average delay from onset of recognisable symptoms of antibody deficiency to diagnosis was six and a half years.[7] Consequences of a delayed diagnosis may be serious. In a study of 32 patients with primary antibody immunodeficiency, more than two thirds experienced diagnostic delay leading to serious morbidity.[8] In any patient with common variable immunodeficiency syndrome, the following complications must be considered: recurrent infections and autoimmune phenomena. Therefore, it is of great importance that diagnosis of common variable immunodeficiency syndrome be made early.[9]

Significance of early diagnosis[9]

1 Patients need appropriate antibiotics in maximum dosages for at least 14 days.
2 It is helpful in counselling patients, both in explaining symptoms and in planning future management. Genetic counselling is also required for certain immunodeficiency diagnosis.
3 Immunoglobulin replacement therapy is available for antibody deficiency.
4 Early diagnosis prevents irreversible organ damage.
5 There is an increased incidence of malignancy and autoimmune diseases in these patients.[9]

Ten warning signs of primary immunodeficiency (Jeffry Model Foundation)[9]

Cooney *et al.* have provided a set of 10 warning signs to raise the suspicion of primary immunodeficiency.[9]

1 Eight or more new ear infections within one year.
2 Two or more serious sinus infections within one year.
3 Two or more months on antibiotics with little effect.
4 Two or more pneumonias within one year.
5 Failure of an infant to gain weight or grow normally.
6 Recurrent deep skin or organ abscesses.
7 Persistent thrush in mouth or elsewhere on skin after age one.
8 Need for intravenous antibiotics to clear infections.
9 Two or more deep-seated infections.
10 A family history of primary immunodeficiency.

https://doi.org/10.1017/S002221510700014X Published online by Cambridge University Press

Conclusion

Despite the general availability of immunological diagnostic techniques, common variable immunodeficiency syndrome still continues to be diagnosed late.[8] Sometimes patients can present with totally atypical symptoms. There is widespread ignorance about the importance of major immunoglobulin deficiencies and their association with recurrent bacterial infections particularly in adults.

Since early diagnosis and efficient immunoglobulin prophylaxis can prevent the serious complications, it is essential to exclude the diagnosis early in the investigation of any patient with repeated bacterial infections.[10] It is necessary to increase awareness of this condition and to raise the index of suspicion based upon the warning signs outlined above.

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Dr C Spyridakou takes responsibility for the integrity of the content of the paper.
Competing interests: None declared