

Novel biochemical markers of granulomatous disease in common variable immunodeficiency in a child with arthritis

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Key Words: Common variable immunodeficiency, chitotriosidase, granulomatous disease, glycosaminoglycans, sarcoidosis

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Abstract

Common variable immunodeficiency (CVID) may be associated with non-caseating granulomatous disease, and this feature may be confused with idiopathic sarcoidosis. We report a child with hypertonicity of central origin and inflammatory arthritis that manifested in the first 5 years of life, who developed CVID with hepatic granulomatous disease at the age of 13 years. Biochemical analysis revealed significantly elevated levels of serum chitotriosidase, an elevated serum angiotensin converting enzyme (ACE) and increased urinary glycosaminoglycan excretion. These features are recognised in idiopathic sarcoidosis, but have never previously been reported in CVID associated granulomatous disease. Following treatment with intravenous immunoglobulin and oral corticosteroids the ACE level returned to normal, and there has been a significant reduction in the level of serum chitotriosidase and urinary glycosaminoglycans. We hypothesize that serial measurements of serum chitotriosidase, serum angiotensin converting enzyme and urinary glycosaminoglycans may provide useful information about granulomatous disease activity in CVID and any response to treatment.

Introduction

A caucasian infant boy born to a non-consanguineous couple presented with a left-sided hemiparesis at seven months of age. He had an unremarkable perinatal period. A computerised tomography (CT) scan of the brain done at one year of age revealed a right-sided peripheral infarct with hemi-atrophy. It was deemed to be non-progressive and he was treated by a multidisciplinary team within the child development center. He developed severe fixed flexion deformities of both hips and knees at three years of age for which tendon release was unsuccessful.

An inflammatory arthropathy was diagnosed at four years of age with pain and swelling of the right wrist, right metacarpophalangeal joints, and the fourth and fifth metatarsophalangeal joints of both feet. Contractures subsequently developed at both wrists and elbows. Investigations showed that he was positive for the HLA B27 antigen, although this was of uncertain significance in terms of his clinical pattern of inflammatory arthritis. His serum immunoglobulins were normal at this time. He was treated with non-steroidal anti-inflammatory drugs and physiotherapy. At seven years of age, he had an episode of idiopathic thrombocytopenic purpura with a platelet count of 57×10^9 /Litre. This resolved uneventfully with conservative management. He was subsequently lost to rheumatology follow up for several years.

He re-presented following a routine school health examination at the age of thirteen years with pallor and massive splenomegaly. The family had not noted any change in his abdominal appearance, suggesting the splenomegaly was chronic. He had a history of frequent upper respiratory infections associated with muco-purulent discharge, but he had never been hospitalized with serious infection.

On examination the spleen was palpable ten centimetres below the left sub-costal margin and the liver four centimetres below the right sub-costal margin. He had clinically insignificant enlargement of the inguinal lymph nodes. Abdominal ultrasound revealed smooth hepatosplenomegaly with no evidence of portal hypertension. Abdominal CT scan confirmed the splenomegaly and did not show evidence of radiologically sinister lymph nodes. Magnetic resonance imaging of the brain showed a neuronal migration disorder, which after further investigations documented below was deemed consistent with an unspecified antenatal insult. There was now a global reduction in immunoglobulin levels and functional antibodies were negative to *haemophilus influenzae type b*, *pneumococcus* and *tetanus*. These and other relevant preliminary investigations are shown in Table 1.

Table 1. Preliminary investigations in a boy with CVID

Hemoglobin	7.3 g/dL
White cell count	2.96 x 10 ⁹ /L Neutrophils -1.64 x 10 (9) / L Lymphocytes – 1.06 x 10 (9)/L
Platelets	128 x 10 ⁹ /L
Blood film	Hypochromic microcytic anemia with poikilocytosis
Immunoglobulin G	2.41 g/L (Normal 6.13 – 15.5)
Immunoglobulin A	< 0.067 g/L (Normal 0.44 – 2.63)
Immunoglobulin M	0.11 g/L (Normal 0.47 – 2.57)
Immunoglobulin G1	1.88 g/L (Normal 4.22 - 12.9)
Immunoglobulin G2	< 0.09 g/L (Normal 1.17 - 7.47)
Immunoglobulin G3	0.5 g/L (Normal 0.41 - 1.29)
Immunoglobulin G4	< 0.01 g/L (Normal 0.01 - 2.91)
Bone marrow examination	Mildly dysplastic marrow with all cell lines represented. Some features of myeloproliferative and myelodysplastic disorders but non-diagnostic. Cytogenetic analysis normal.

A liver biopsy showed multiple non-caseating granulomas, and serum angiotensin converting enzyme was elevated at 159 units/Litre (range 18-66). He had no accessible lymph nodes to biopsy. White cell enzymes requested to investigate a possible storage disorder showed a grossly elevated level of chitotriosidase at 2664 µmol/L (range 4 – 80). Urine glycosaminoglycans were also elevated at 25.6 mg/mM Cr (range 3.4-10.6), and chromatography showed increased heparan and chondroitin sulphate. Screening for purine nucleotide deficiency was normal, and the patient had a normal level of signalling lymphocyte activating molecule (SLAM) associated protein, thereby excluding X-linked lymphoproliferative disease. He had no evidence of acute viral infection with Epstein-Barr, adenovirus, parvovirus and CMV. Relevant second phase investigations are shown in Table 2.

Table 2. Second phase of investigations in a boy with CVID

<u>Investigation</u>	<u>Result</u>	<u>Comment</u>
White cell enzymes	Chitotriosidase 2664 µmol/L (Normal 4 – 80)	Elevated levels are seen in sarcoidosis and storage disorders such as Gaucher's disease
Urinary glycosaminoglycans	25.6 mg / ml (Normal 3.4 – 10.6)	Increased heparan and chondroitin sulphate Elevated in sarcoidosis
Serum Angiotensin Converting Enzyme	159 Units/L (Normal 18 – 66)	
Liver biopsy	Multiple non-caseating granulomas of the sarcoidal type	
Ophthalmology screen	Negative	
Muscle biopsy	Non diagnostic rod-like structures	
DNA from peripheral lymphocytes	Negative for mitochondrial mutations	

With the exclusion of other conditions, the presence of hypogammaglobulinaemia and absent functional antibodies were typical of CVID. The patient was started on intravenous immunoglobulin (IVIG) replacement every three weeks at a dose of 400mg/kg. Because of the hepatic granulomas, he was treated simultaneously with corticosteroids and prophylactic cotrimoxazole. He has had no further episodes of respiratory sepsis since commencing therapy and his splenomegaly has improved. He has a normal full blood count. His serum ACE has returned to normal, and most recent serum chitotriosidase is significantly reduced at 148 µmol/L.H. The urinary glycosaminoglycans have fallen and are now modestly increased at 18.6 mg/mM Cr.

Discussion

Combined variable immunodeficiency (CVID) relates to a heterogeneous group of disorders in which antibody deficiency is always present and there may be a variable degree of cell-mediated immune defect. Autoimmune diseases are common in patients with CVID, and a multisystem non-caseating granulomatous disease is seen in about 10% (1). CVID is the most prevalent primary immunodeficiency in late childhood and adulthood (2). The incidence is approximately 1 in 50,000. There is no predilection for any specific race and no sex preponderance. The peak age of onset is in children aged 1-5 years and in persons aged 16-20 years, but it can occur in any age group.

CVID is a disorder associated with defective antibody function as a result of both B-cell and T-cell dysfunction (1). Bacterial infections, particularly of the respiratory and gastrointestinal tract, are frequent. However, CVID is diverse both in clinical presentation and types of deficiency. Although decreased serum levels of IgG and IgA are characteristic, approximately 50% of patients also have diminished serum IgM and T lymphocyte dysfunction. The B cells may fail to mature possibly as a result of T cell dysfunction. In addition to infection risk, autoimmune disease (rheumatoid arthritis, vitiligo, hemolytic anemia, pernicious anaemia, thrombocytopenia, auto-immune hepatitis and primary biliary cirrhosis) and malignancy (including lymphomas of B cell phenotype, gastric carcinoma and malignant melanomas) are more common in patients with CVID. The general management is immunoglobulin replacement, with vigilance for infection, and therapy for organ specific auto-immune disease as required.

In patients with CVID, non-necrotising granulomas (sarcoid-like) are recognised (3). Chitotriosidase is a chitinase that is massively expressed by lipid-laden tissue macrophage in man, and is elevated in patients with sarcoidosis (4). Its enzymatic activity is also elevated in serum of patients suffering from Gaucher's disease (5) and may have a role as a monitor of therapeutic intervention (6). Elevated chitotriosidase is also seen in visceral Leishmaniasis (6), and thalassaemia (7). Levels of chitotriosidase were elevated in our patient prior to treatment with intravenous immunoglobulin (IVIG) and corticosteroid. Approximately 10 months after therapy the level of chitotriosidase has reduced significantly, suggesting reduction in granulomatous disease activity. Our patient had other biochemical features of interest. He had elevated levels of urinary glycosaminoglycans, which are known to be shed by granuloma cells and may have an immunomodulatory function (8). He had an elevated level of ACE which has also returned to normal with treatment, consistent with previous reports (9).

Conclusion

We hypothesize that serum chitotriosidase, serum angiotensin converting enzyme and urinary glycosaminoglycans could be potential novel biochemical markers for granulomatous disease in CVID. This finding needs to be confirmed in other patients. If serum chitotriosidase is elevated in a patient with CVID, we suggest this should prompt investigations for evidence of granulomata, and that serial measurements of the enzymatic activity may help in monitoring subsequent therapeutic intervention.

Acknowledgements

The following provided valuable assistance with the clinical management of this patient. Dr R Appleton, Dr D Isherwood, Dr E Carroll, Dr M Ashworth, Dr P Arkwright, (all of the Royal Liverpool Children's Hospital, UK), Dr M Abinun (Newcastle General Infirmary, UK).

References

1. Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. *Blood*. 2002;99:2694-2702
2. Rosen FS, Cooper MD, Wedgewood RJ. The primary immune deficiencies. *N Engl J Med* 1995; 333: 421-40
3. Sutor G-S, Fabel H. Sarcoidosis and common variable immunodeficiency. *Respiration* 2000;67:204-208
4. Aguilera B, Ghauharali K, Helmond TJ et al. Transglycosidase activity of chitotriosidase. *J Biol Chem* 2003; 278(42):40911-6.
5. Aerts JM and Hollack CE. *Ballieres Clin Haematol* 1997; 10: 691-709
6. Hollack CE, van Weely S, van Oers MH, Aerts JM. *J Clin Invest* 1994;93:1288-1292
7. Barone R, Di Gregorio F, Romeo MA, Schiliro G, and Pavone L. *Blood Cells Mol. Dis.* 1999; 25: 1-8
8. DePrisco G, Bandel C, Cockerell CJ, Ehrig T. Interstitial heparan sulfate in granulomatous inflammatory skin diseases. *J Am Acad Dermatol.* 2004;50(2):253-7
9. Fasano MB, Sullivan KE, Sarpong SB et al. Sarcoidosis and Common Variable Immunodeficiency. *Medicine (Baltimore)*. 1996 Sep;75(5):251-61.