

IMMUNODEFICIENCY DISEASES PRESENTING IN ADULTS – DIAGNOSIS AND MANAGEMENT

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ABSTRACT

In adults with recurrent regional infections, it is mandatory to exclude an underlying predisposing anatomical defect. Secondary causes of immune deficiency are the commonest cause in adults presenting with recurrent infections. Primary immune deficiency can present for the first time in adults; as in children, failure to consider this diagnosis remains a major cause of diagnostic delay. Common variable immune deficiency (CVID) is the commonest antibody deficiency seen in adults. An approach to diagnosis is suggested with relevant screening tests based on the clinical picture, to be followed by further advanced assays where required. A multidisciplinary team approach is advocated in the management of patients with immune deficiency. Rapid advances in immunology hold the promise of dissecting primary immune deficiency and also of uncovering immune defects in clinical situations where reasons for recurrent infections are currently unexplained.

INTRODUCTION

Immune deficiency in adult patients generally presents with recurrent infections, and these patients are frequently referred to a clinical immunologist for evaluation of their immune status. In general terms, adult patients with recurrent infections due to underlying immune deficiency fall into one of the following three groups:

1. Patients with a known inherited genetic disorder resulting in primary immune deficiency that was diagnosed in childhood.
2. Secondary immune deficiency due to underlying disease, or due to a complication of therapy.
3. Late-onset primary immune disorder presenting for the first time in adulthood.

This brief overview focuses on practical aspects of the investigation and management of these patients.

CHILDHOOD PRIMARY IMMUNE DEFICIENCY

A wide variety of primary immune disorders presenting in childhood can persist into adulthood; these have been reviewed by Brian Eley and Monika Esser elsewhere in this edition. It is also important to remember

that rare disorders such as cystic fibrosis and chronic granulomatous disease (CGD) can present for the first time in adults. Adenosine deaminase (ADA) deficiency typically causes severe combined immunodeficiency (SCID) in infants, but can rarely present in older patients with immune deficiency and unexplained lymphopenia, and may have associated autoimmunity and hepatobiliary disease.¹

SECONDARY IMMUNE DEFICIENCY

When faced with an adult presenting with recurrent infections, immune deficiency secondary to a variety of disorders should be considered, and these need to be excluded. The conditions listed in Table I represent the commonest reason for recurrent infections occurring in adults, and the diagnosis is usually readily evident from the clinical evaluation together with select laboratory tests.

Table I. Acquired, secondary causes of immune deficiency

HIV infection
Diabetes
Chronic renal disease – especially nephrotic syndrome
Chronic liver disease – cirrhosis
Haematological disorders: chronic lymphocytic leukaemia, myeloma, lymphoma
Immune suppression due to radiation, cytotoxic and/or steroid therapy
Malnutrition, vitamin and mineral deficiency, e.g. zinc deficiency
Autoimmune disorders, e.g. systemic lupus erythematosus
Intestinal lymphangiectasia resulting in immunoglobulin and lymphocyte loss
Environmental exposure to chemicals and 'xenobiotics'
Thymoma with hypogammaglobulinaemia – Good's syndrome

PRIMARY IMMUNE DISEASES IN ADULTS

Defects in humeral immunity

IgA deficiency

Isolated IgA deficiency is common in Europe, with textbooks quoting a prevalence of 1 in 700 of the population.² The condition is far less common in blacks and Asians, and while comprehensive figures for all of the South African populations are not available, the prevalence of IgA deficiency among blood donors in KwaZulu-Natal and Brazil is comparable to that of western populations.³ Most patients with IgA deficiency are asymptomatic and it is thought that associated immune defects, such as IgG subclass deficiency, may account for those presenting with recurrent infections.

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Abnormalities in serum IgM levels

In contrast to IgA deficiency, isolated IgM deficiency is extremely rare. There are, however, analogies with IgA deficiency in that IgM deficiency can be an incidental finding in otherwise asymptomatic people (or appear unrelated to their presenting illness),⁴ or patients may present with severe infections with polysaccharide-containing organisms such as pneumococci, *Haemophilus influenzae*, meningococci and *Pseudomonas*.⁵ It has been speculated that IgM may be more important for protection in childhood than in late adulthood, where secondary antigenic challenge induces a brisk IgG response.⁴

Patients with hyper-IgM usually present in childhood with a primary immunodeficiency with elevated serum IgM but reduced IgG and IgA levels.⁶ This is a genetically heterogeneous disorder but the essential defect is in CD40-mediated signalling causing defective monocyte, B-cell and T-cell function. This results in recurrent bacterial and opportunistic infections due to *Pneumocystis* and *Cryptosporidium* organisms. Milder mutations can rarely result in a less severe clinical course that can present later in life.⁶

Late-onset hypogammaglobulinaemia

Common variable hypogammaglobulinaemia (CVH) is also known as common variable immune deficiency (CVID). It can present at any age after childhood, typically with recurrent upper respiratory tract infections or pneumonia, or with chronic diarrhoea and malabsorption due to IgA deficiency resulting in gastrointestinal colonisation by *Giardia lamblia*. It was the commonest primary immune deficiency in adults in a recent published series from Iran⁷ affecting 28 of 55 patients (51%). This is remarkably similar to a recent survey in USA where CVID accounted for 52% of surveyed patients,⁸ and anecdotal local experience accords with these publications (unpublished observation).

Defects in cellular immunity

Patients present far less commonly with primary defects in cellular immunity in adults. The most common situation is where defects in cellular immunity accompany hypogammaglobulinaemia in CVID; in a large series this was documented in 40% of 248 cases.⁹ Patients with acquired antibodies to interferon (IFN)- γ are increasingly being described¹⁰ and defects in the interleukin (IL)-12 or IFN- γ type 1 cytokine pathway

can present with disseminated *Mycobacterium avium* or *Salmonella* infections,¹¹

IgG subclass deficiency

Analogous to IgA deficiency, patients with IgG subclass deficiency may be asymptomatic or present with recurrent sinopulmonary infections. IgG1 and IgG3 subclass deficiency is more common in adults.¹²

Defects in phagocytosis

These have recently been reviewed.¹³ They are usually diagnosed in childhood with severe or recurrent infections involving nonpathogenic bacteria or fungi, but they can also present in adults.

INVESTIGATION AND DIAGNOSIS

Failure to consider the diagnosis of underlying primary immune deficiency remains a major cause of diagnostic delay and resultant patient morbidity. Efforts have been made to facilitate earlier diagnosis by promoting diagnostic protocols for use by both adult physicians and paediatricians in Europe.¹⁴

From the clinical presentation it is usually possible to identify the component of the immune system that is involved (Fig. 1). Recurrent localised infections are invariably due to defects in anatomical barriers leading to chronic infections. A good example of this is recurrent pneumococcal meningitis following fractures of the basal skull. Defects in innate immunity can cause recurrent infections; the most commonly encountered example is recurrent viral infection (especially herpes) due to deficiency of natural killer (NK) cells.^{15,16} Patients with deficiency of terminal complement components C7-9 present with recurrent *Neisseria meningitidis* meningitis. Defects in antibody production present with recurrent upper respiratory, sinus and middle-ear infections (in younger patients). Defects in T-cell function present with typical opportunistic organisms, fungal, parasitic and mycobacterial infections. Defects in phagocytic function can present with infections due to non-pathogenic bacteria or fungi. Finally, defects in complement components can present with either recurrent infection or autoimmune disease. An example of the latter is C3-deficiency with systemic lupus erythematosus as the clinical presentation.

An outline of the approach to investigations is provided in Figure 2, which suggests an initial screening test for evaluation of each of the components of the immune system suspected to be involved, with further second-level and advanced tests to be performed where relevant.¹⁷ Quantisation of the major immunoglobulin classes IgA, IgM and IgG is routinely requested as the initial investigation in cases of suspected humeral immune deficiency. Where panhypogammaglobulinaemia is documented the diagnosis is usually CVID, provided haematological diseases such as myeloma and chronic lymphocytic leukaemia (CLL) can be excluded. Where immunoglobulin levels are low-normal and/or an IgG subclass deficiency is suspected, it is customary to request serum IgG antibody levels against type-specific capsular polysaccharides of pneumococcus, and against tetanus toxoid as representative of a protein antigen. If these are low, the response to vaccination with pneumococcus and/or tetanus toxoid is evaluated after 4-6 weeks. NK cells are measured by flow cytometry and specifically defined as the CD3⁺ CD16⁺56⁺ subset. It would be impor-

Patient with Recurrent Infections: ? Immune component involved	
IMMUNE	CLINICAL
1. Anatomical defect	Localised infections
2. NK cell	Recurrent viral
3. B-cell	Sinus/URTI/Pneumonia
4. T-cell	Protozoa/fungi/mycobacteriae
5. Phagocytic	Sup. skin or systemic infections: low grade organisms
4. Complement	Infections/autoimmunity

NK = natural killer, Sup. = superficial

Fig. 1. Investigation of immune components involved in patients with recurrent infection.

Investigation – Immune deficiency*

	INITIAL SCREEN	2ND LEVEL	ADVANCED
1. B-cell	*Quantify IgA/G/M *Immunization AB's: DT, rubella, ABO	*B-cell number *Ab's: vaccinate T.Toxoid Pneumococcus	IgG subclasses
2. T-cell	*LS count *Skin DTH	CD3/4/8/NK/B-cell LS function: ag/mitogen	Cytokines Cytotoxicity IL-12R/IFN- γ R IFN- γ antibody
3. Phag.	NBT		Chemotaxis Resp. Burst Phagocytic index
4. Complem.	CH50/C3/C4		Individual complem levels

Abbreviations: AB's = antibodies, DT = diphtheria and tetanus, LS = lymphocyte, DTH = delayed-type hypersensitivity, Resp. = respiratory, Phag = phagocytic, Complem = complement, CH50 = total haemolytic activity, NBT = nitroblue tetrazolium test, ag = antigen

* Modified from Cunningham-Rundles.¹⁷

Fig. 2. Investigations for immune deficiency.

tant to confirm any reduction in numbers of NK cells in a functional assay; operationally this is done by measuring the cytolytic capacity of fresh NK cells against K562 erythroleukaemic tumour cell line. If defects in phagocytic function are suspected, this can be evaluated by flow cytometry to measure phagocytic index and respiratory burst of polymorph neutrophils and monocytes. A full evaluation includes assessment of bacterial killing and leukocyte chemotaxis. Assessment of T-cell function is more complex. Delayed-type hypersensitivity testing remains a useful indicator of *in vivo* T-cell function, especially if several antigens are used which enables one to document anergy. Measurement of peripheral blood subsets provides information on the percentage and absolute numbers of circulating T-cell, B-cell and NK cells, and is currently performed as a single platform by flow cytometry. Proliferative responses to non-specific stimulation by mitogens (phytohaemagglutinin (PHA)/Con-A or phorbol ester/ionomycin) provide limited physiological information but can indicate grossly impaired T-cell function. In the presence of normal mitogenic responses, stimulation by antigens can provide more relevant functional information but requires a panel of recall antigens such as tetanus toxoid, streptococcal antigen, purified protein derivative (PPD) and *Candida*, as well as some experience to interpret the results. Finally, more sophisticated assays may occasionally be required. These include measurement of Th-1/Th-2 cytokine balance and evaluation of NK, CD4⁺ and CD8⁺ killing in functional cytolytic assays.^{18,19}

Where proliferative responses are normal and an inhibitor of IFN- γ is suspected, such as in the case of disseminated avium infection in an otherwise normal individual, it is imperative to specifically test for a serum autoantibody against IFN- γ .¹⁰

MANAGEMENT

Patients with CVID need monthly intravenous immunoglobulin (IVIg) replacement in order to prevent chronic lung damage from recurrent infections, which can result in bronchiectasis. These patients frequently suffer from giardiasis and resultant malabsorption. They are best managed by a multidisciplinary team consisting of a clinical immunologist, a pulmonologist and a gastroenterologist. Baseline immunoglobulin levels, hepatitis screen, and HIV status must be documented. Anti-IgA antibodies may be present in patients with markedly reduced serum IgA, and can cause anaphylaxis. In these cases immunoglobulin preparations that are low in IgA can be used. CVID patients are also at risk of a number of complications. These include a range of gastrointestinal diseases (inflammatory bowel disease, protein-losing enteropathy, sprue-like disease, lymphangiectasia), malignancies, lymphoma, and autoimmunity.^{9,20} In patients with normal or low-normal immunoglobulin levels having recurrent infections, careful evaluation for evidence of impaired antibody production in response to vaccination is required before instituting IVIg therapy, since the latter is costly, can be associated with side-effects, and is usually lifelong. Patients with disseminated avium infections who have demonstrable antibodies to IFN- γ may benefit from adjunctive parenteral IFN- γ therapy.¹⁰

FUTURE DEVELOPMENTS

Immunology is a complex field. Rapid advances in understanding of immunity together with advances in technology are providing new methods of evaluating immune function, such as polychromatic flow cytometry, where the use of up to 17 fluorochromes permits the simultaneous evaluation of multiple cell surface markers and intracellular cytokines, allowing correlation

with memory T-cell phenotypes.¹⁸ These are yielding greater understanding in chronic viral infections, e.g. the demonstration of skewing of memory T-cell subsets in HIV rapid progressors.²¹ At the same time, there are extremely rapid advances in the understanding of the regulation of immune responses by regulatory T-cells²² and IL-23/IL-27 pathway,²³ among other pathways of immune regulation. Immune dysregulation due to defective regulatory T-cell function in primary immune deficiencies has also recently been described.²⁴ I anticipate that application of these advances in the future will yield new insights and be of value in the evaluation of adult patients presenting with unusual infections, where currently available relatively crude immune assays usually fail to demonstrate any abnormality.

Declaration of conflict of interest

The author declares no conflict of interest.

REFERENCES

- Ozshahin H, Arredondo-Vega FX, Santisteban I, et al. Adenosine deaminase deficiency in adults. *Blood* 1997; **89**: 2849-2855.
- Russel MW, Kilian M. Biological activities of IgA. In: Mestecky J, Lamm ME, Strober W, Bienenstock J, McGhee JR, Mayer L, eds. *Mucosal Immunology*, 3rd ed. Elsevier Academic Press, 2005: 267-290
- Hattingh C, Green F, Bubb MD, Conradie JD. The incidence of IgA deficiency amongst blood donors in Kwazulu-Natal. *S Afr J Sci* 1996; **92**: 206-209.
- Ross IN, Thompson RA. Severe selective IgM deficiency. *J Clin Path* 1976; **29**: 773-777.
- Zaka-ur-Rab Z, Gupta P. Pseudomonas septicaemia in selective IgM deficiency. *Indian Pediatrics* 2005; **42**: 961-962.
- Notarangelo LD, Lanzi G, Peron S, Durandy A. Defects of class-switch recombination. *J Allergy Clin Immunol* 2006; **117**: 855-864.
- Mansouri D, Adimi P, Mirsaedi M, et al. Primary immune deficiencies presenting in adults: seven years of experience from Iran. *J Clin Immunol* 2005; **25**: 385-391.
- Boyle J. Characteristics of health outcomes of patients with primary immune deficiency diseases in the United States. *J Allergy Clin Immunol* 2004; **113**: S43.
- Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. *Clin Immunol* 1999; **92**: 34-48.
- Kampmann B, Hemingway C, Stephens A, et al. Acquired predisposition to mycobacterial disease due to autoantibodies to IFN- γ . *J Clin Invest* 2005; **115**: 2480-2488.
- Lammas DA, Drysdale P, Ben-Smith A, et al. Diagnosis of defects in the type 1 cytokine pathway. *Microbes Infect* 2000; **2**: 1567-1578.
- Soderstrom T, Soderstrom R, Avanzi A, et al. Immunoglobulin G subclass deficiencies. *Int Arch Allergy Appl Immunol* 1987; **82**: 476.
- Lekstrom-Himes JA, Gallin JI. Immunodeficiency diseases caused by defects in phagocytes. *N Engl J Med* 2000; **343**: 1703-1714.
- De Vries E. Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. *Clin Exp Immunol* 2006; **145**: 204-214.
- Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu Rev Immunol* 1999; **17**: 189-220.
- Orange JS. Human natural killer cell deficiencies and susceptibility to infection. *Microbes Infect* 2002; **2**: 1545-1558.
- Cunningham-Rundles C. Immune deficiency: office evaluation and treatment. *Allergy Asthma Proc* 2003; **24**: 409-415.
- Casazza JP, Betts MR, Price DA, et al. Acquisition of direct antiviral effector functions by CMV-specific CD4+ T lymphocytes with cellular maturation. *J Exp Med* 2007; **203**: 2865-2877.
- Hatam L, Schuval S, Bonagura VR. Flow cytometric analysis of natural killer cell function as a clinical assay. *Cytometry* 1994; **16**: 59-68.
- Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. *Blood* 2002; **99**: 2694-2702.
- Zhang JY, Zhang Z, Wang X, et al. PD-1 up-regulation is correlated with HIV-specific memory CD8+ T-cell exhaustion in typical progressors but not in long-term nonprogressors. *Blood* 2007; **109**: 4671-4678.
- Chess L, Jiang H. Regulation of immune responses by T cells. *N Engl J Med* 2006; **354**: 1166-1176.
- Kastelein RA, Hunter CA, Cua DJ. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. *Annu Rev Immunol* 2007; **25**: 221-242.
- Torgerson, TR, Ochs HD. Regulatory T cells in primary immunodeficiency diseases. *Curr Opin Allergy Clin Immunol* 2007; **7**: 515-521.

Clinical Immunology: Principles and Practice, 3/e

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Edited by RR Rich, TA Fleisher, WT Shearer, H W Schroeder II, A J Frew and CM Weyand

April 2008, hardcover, approx. 1616 pp, 700 illus., 203 x 254 mm, R3 800

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