Medical Algorithm: Diagnosis and Management of Antibody Immunodeficiencies

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AS prepared the concept and wrote the manuscript, TM edited Figures and wrote the manuscript, JL designed Figures and revised manuscript, IQ designed Figures and revised the manuscript, IM revised manuscript, SB revised manuscript, SJ edited Figures and wrote the manuscript.

Background

Primary antibody deficiencies (PAD) constitute the majority of all primary immunodeficiency diseases (PID) also termed inborn errors of immunity (IEI). This category (PAD) represents around 52% of all IEI and the proportion overall is still greater given that antibody deficiency is a component of other groups including combined and severe combined immunodeficiencies (SCID), autoinflammatory disorders, diseases of immune dysregulation and other well defined PIDs (1,2). Secondary antibody deficiencies (SAD) represent a larger and expanding number of individuals resulting from the use of a wide range of immunosuppressive therapies, in particular those targeting B cells, and may also result from renal or gastrointestinal immunoglobulin losses, infections, for example HIV or malaria, malnutrition or others (3).

The manifestations of PAD are protean and encompass a range of infectious and non-infectious complications, including autoimmune, lymphoproliferative, granulomatous and allergy manifestations due to an immunedysregulation, and increased risk of malignancy in some forms of PAD (4,5).

Diagnosis

The diagnosis is based on a combination of clinical features together with laboratory findings, potentially a positive family history and increasingly, genetic testing. The clinical presentation for antibody deficiency is often characterised by recurrent sinopulmonary infections which often take longer to resolve and require prolonged or intravenous antibiotic courses. In addition to the infections presentations, complications may include autoimmune cytopenias, lymphoproliferation, non-infectious inflammation and allergy linked to underlying immune dysregulation. PAD disorders are also linked to an increase risk of malignancy, in particular lymphoma and gastric cancers (4,6). Similar clinical presentations may accompany secondary immunodeficiencies, which must be considered in the differential diagnosis (3). SAD occur more often than inherited antibody deficiencies, and are usually multifactorial, related to an underlying disease or treatment, including growing range of B cell-targeting therapeutics. SAD may also occur as a result of immunoglobulin loss especially via urogenital or gastrointestinal tract. The „leaky gut syndrome“ might be an integral part of some inborn errors of immunity, especially those associated with immune dysregulation, or might accompany other chronic inflammatory diseases. As with all secondary deficiencies, the

search for the primary cause is essential. Both B and T cell functions are typically retained in SAD, although the numbers of CD4 + T cells in particular may be reduced by their intestinal loss. In SAD, there is usually no skewing in B cell subpopulations towards less mature forms and production of specific (postvaccination) antibodies is preserved particularly in SAD caused by protein loss.

The initial laboratory assessment of antibody deficiency consists of determining the concentrations of serum immunoglobulins, including IgG, IgA and IgM alongside the functional investigation of vaccine responses and lymphocyte enumeration, particularly the B cells (Figure 1). Impaired postvaccination response is a characteristic finding in antibody deficiencies. The response to tetanus vaccine verifies a response to protein antigens, while the response elicited by the Pneumovax polysaccharide vaccine (or an alternative vaccine without protein adjuvant) is used to determine immune reaction to polysaccharide antigens.

The decreased antibody levels in very young children, especially in the first year of life, may only represent a delayed development of immunoglobulin production, such as in premature infants or in transient hypogammaglobulinaemia in infancy (Fig. 1). If a reduction of immunoglobulin levels is profound and associated with clinical symptoms, a prompt referral to a specialized immunological examination is required without delay to rule out congenital immunodeficiency. In addition to a detailed examination of antibodies, such investigations include specific B cell and T cell panels designed for the diagnosis of inborn errors of immunity. Combined TREC/KREC screening, originally designed for early diagnosis of SCID, would also detect severe inborn antibody deficiencies, and is being tested in pilot studies or considered for implementation in some countries (8).

The commonest clinically relevant primary antibody deficiency in adults is Common variable immunodeficiency (CVID). Its diagnostic criteria are regularly revised and published as an international consensus (7). Genetic testing has become pivotal for optimization and personalisation of therapy in cases, in which the molecular diagnosis allows a pathway-specific targeted therapeutical approach. An example of this is the use of abatacept, a soluble fusion protein, in cytotoxic T-lymphocyte-associated protein 4 deficiency. There have also been major advances in the screening of newborns using TREC and KREC assays and in adults using calculated globulin (8,9)

Management

In patients with PAD, immunoglobulin replacement therapy (IgRT) represents the mainstay of therapy for many patients (10,11) (Figure 2). The decision to commence IgRT is straight-forward in well-defined PAD with a significant infection burden and supportive laboratory findings - hypogammaglobulinaemia with impaired response to vaccination. The decision becomes somewhat more complex if the manifestation is milder or incompletely pronounced, for instance in cases with hypogammaglobulinaemia but preserved vaccine responses, or in specific antibody deficiency.

IgRT may be administered either intravenously, subcutaneously or as a facilitated subcutaneous infusion using hyaluronidase, and the decisions regarding route, frequency of administration and site of administration, whether home or hospital, are individual and are composed jointly with the patient and medical team (12). In general, IgRT is commenced based on weight at 0.4 – 0.6g/kg/month of IgG. It is adjusted individually according to the clinical status, such as infection burden, bronchiectasis, type of PAD and other complications, as well as to the laboratory parameters, including trough IgG level aiming for >7g/L. This however, varies between centres and countries (13,14). A careful assessment and monitoring is required during IgRT with regard to clinical condition and non-infectious complications. In a number of circumstances, antibiotic prophylaxis may be used, for instance in milder immunodeficiencies with a less severe infectious susceptibility, such as IgG subclass deficiency, combined IgA deficiency with IgG subclass deficiency or specific antibody deficiency. Moreover, antibiotics may be prescribed in addition to IgRT, should the patients fail to respond to optimally individualised IgRT or in those with existing end-organ damage such as bronchiectasis, chronic sinusitis or in those colonised with *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia*. Antibiotic regimens will vary according to the setting, organism and sensitivities. In general, in adult PAD patients with frequent respiratory tract infections on IgRT, who may also have bronchiectasis, azithromycin 250-500mg three days/week has been shown to decrease infective exacerbations. In patients with concomitant T cell or neutrophil impairment, such as combined or severe combined immunodeficiency, hyper IgM syndrome, CVID and others, cotrimoxazole may be considered (10,15). PAD patients require regular follow up both to monitor therapy and for early detection and management of complications (4,5,16,17). Laboratory and radiological monitoring are individualised; baseline testing includes full blood count, renal and liver functions and C-reactive protein assessment 2-4 times yearly , with LDH, β2 microglobulin in lymphoma

prevention, lymphocyte subsets 1-2 times yearly, abdomen ultrasonography, neck ultrasonography if lymphadenopathy is investigated, chest X-ray and lung function tests once a year. In CVID or other forms of PAD with severe lung or gastrointestinal (GIT) involvement, chest computed tomography imaging every 3-5 years and screening GIT endoscopies every 1-2 years, respectively, are recommended in some centres (18).

Diagnosis and management of PAD are continuously improving, thanks to better immunologic and molecular-genetic diagnostic tools, broader options for individually-tailored IgRT, personalised pathway-specific therapies and greater knowledge of the role of haemopoietic stem cell transplantation and gene therapy/editing in management of PAD.

Acknowledgement:

Dr.Sediva and Dr.Milota were supported by the Czech Ministry of Health grant AZV NV18-05-00162.

Dr. Sediva reports grants from Motol University Hospital, personal fees from Takeda, personal fees from Octapharma, personal fees from CSL Behring, during the conduct of the study; Dr. Milota has nothing to disclose. Dr.Litzman reports personal fees from Octapharma and Takeda. Dr. Quinti reports other from null, outside the submitted work; Dr. Meyts reports grants from CSL Behring , outside the submitted work. Dr. Burns reports grants from NIHR, grants from UCLH III BRC, grants from UKRI/ MRC, grants from GOSH/ICH BRC, personal fees from Immunodeficiency Canada/IAACI, non-financial support from CSL Behring, from Baxalta, personal fees from Biotest, grants from Wellcome Trust, grants from Rosetrees Foundation, grants from Jeffrey Modell Foundation, during the conduct of the study; Dr. Jolles reports grants, personal fees and other from CSL Behring, grants, personal fees and other from Octapharma, grants, personal fees and other from Takeda, personal fees and other from LFB, personal fees and other from Grifols, personal fees and other from Biotest, outside the submitted work.

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Figure 1: Diagnostic algorithm for antibody deficiency (PAD- Primary antibody deficiency, CVID- Common variable immunodeficiency, THI- Transient hypogammaglobulinemia of infancy, SPAD- Specific antibody deficiency, XL- X-linked, AD- Autosomal dominant, AR- Autosomal recessive, GOF- Gain-of-function)

Figure 2: Therapeutic algorithm for antibody deficiency (ATB- Antibiotics, IgRT- Immunoglobulin replacement therapy, AI- Auitoimmune, GLILD- Granulomatous-lymphocytic interstitial lung disease, IBD- Inflammatory bowel disease, LN- Lymph node)