Autoimmune diseases of gastrointestinal tract in children with humoral immunodeficiency – problems of diagnosis

Problemy diagnostyczne w autoimmunizacyjnych schorzeniach przewodu pokarmowego u dzieci z niedoborem odporności humoralnej

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Słowa kluczowe: dzieci, niedobory odporności humoralnej, autoimmunizacja, przewód pokarmowy.

Abstract

The most common humoral immunodeficiencies in children are selected IgA deficiency (IgAD) and common variable immunodeficiency (CVID). IgA deficiency is diagnosed based on laboratory tests because the majority of patients demonstrate no clinical symptoms. Standards for CVID diagnosis include clinical symptoms, hypogammaglobulinemia (IgG and often IgA), weak production of specific antibodies in response to vaccination and disorders of cellular immunity. Humoral immunodeficiencies are associated with autoimmunity in about 30% of cases. Autoimmune diseases in children include hematological (e.g. thrombocytopenia) and gastrointestinal (GI) diseases (mainly celiac and Crohn’s disease). There are no standards of diagnostic procedures of GI autoimmunity in immunodeficiency patients. The screening of GI autoimmunity was performed in all children with humoral immunodeficiencies including detection of antibodies for celiac disease (anti-endomysial, tissue transglutaminase and gliadin), Crohn’s disease (anti-Saccharomyces cerevisiae antigens, pancreatic cells) and ulcerative colitis (anti neutrophils cytoplasm, goblet cells). The lowering of the limit for a positive value of antibodies is postulated to adjust these results to weaker production of antibodies due to immunodeficiency. This screening led to determining a group of children with present antibodies independently of clinical symptoms. Careful monitoring of antibodies and occurrence of clinical symptoms is suggested to diagnose as early as possible concomitant autoimmune disease in children with immunodeficiency.

Streszczenie

Najczęstszymi niedoborami odporności humoralnej u dzieci są izolowany niedobór IgA (IgA deficiency – IgAD) oraz pospolity zmienny niedobór odporności (common variable immunodeficiency – CVID). Rozpoznanie IgAD ustala się na podstawie wyników badań laboratoryjnych, natomiast rozpoznanie CVID opiera się na standardach obejmujących objawy kliniczne i hypogammaglobulinemię (IGG i często IGA), niski poziom swoistych przeciwiciel w odpowiedzi na szczepienia oraz zaburzenia odporności komórkowej. Schorzenia autoimmunizacyjne współistnieją z niedoborami odporności u ok. 30% pacjentów. U dzieci najczęściej stwierdza się zaburzenia hematologiczne (np. malopłytkowość) i schorzenia przewodu pokarmowego, w tym chorobę trzewną i Leśniowskiego-Crohna. Badania przesiewowe w kierunku schorzeń autoimmunizacyjnych przewodu pokarmowego obejmują wykrywanie przeciwicieli typowych dla choroby trzewnej (dla endomysium, transglutaminy, tkankowej i gliadyny), Leśniowskiego-Crohna (dla antigenów Saccharomyces cerevisiae i komórek zewnętrznych rezynki i gładkiej), Leśniowskiego-Crohna (dla antigénów Saccharomyces cerevisiae i komórek zewnętrznych rezynki i gładkiej) oraz wzrostu sklonającego zapalenia jelita grubej (dla cytobazmy granulocytołów, komórek śluzotworczych). Postuluje się obniżenie progu uznania wyników oceny przeciwicieli za dodatnie, aby uwzględnić niedobór odporności. Ocena obecności autoprzeciwciał pozwala na wyselekcjonowanie dzieci z przeciwciałami bez względu na występowanie lub nie objawów klinicznych. Monitorowanie poziomu przeciwiciela oraz występowania objawów klinicznych jest ważne dla wcześniejszego rozpoznania współistniejącej choroby autoimmunizacyjnej u dzieci z niedoborami odporności.
The most common humoral immunodeficiencies in children

Selected IgA deficiency (sIgAD, IgAD)

The frequency of this defect is unknown; estimation of its occurrence from 1 : 400 to 1 : 700 children depends on the country of the study and number of children included in the study group [1]. The majority of children (about 80%) have no clinical symptoms of selected IgA deficiency. The remaining children show recurrent infections of the respiratory and gastrointestinal system. Abdominal pain, problems with jejenum motility (constipation or diarrhea), feeling of discomfort and distention are 10–20 times more frequent in sIgAD than in healthy children in the same age. The lack of secretory IgA produced and secreted by B lymphocytes present in free lymphoid tissue under mucous membrane of the gastrointestinal tract is associated with these symptoms [2–4]. The basic role of secretory IgA is protection of mucous membranes and selection of antigens passing this barrier. Moreover, the secretory IgA inhibits the expression of proinflammatory bacterial epitopes, limiting the presence of bacterial pathogens to special determined regions of the jejenum mucous membrane, preventing the binding of pathogens to epithelial cells and helping in intraepithelial neutralization of pathogens and other bacterial products [5]. In selected IgA deficiency this immunoglobulin is replaced by IgG and IgM. The lack of secretory IgA is associated not only with prolonged inflammatory diseases of the gastrointestinal tract such as atrophic gastritis, Crohn’s disease or celiac disease but also with infections, e.g. *Helicobacter pylori*, *Campylobacter* or *Giardia lamblia*, showing similar symptoms. These infections are more frequent in adults with sIgAD than in children. In the histology of biopsy from people during *Helicobacter pylori* or *Campylobacter* infection, the flattening of jejenum villi suggests celiac disease. However, the effective therapy of infection with antibiotics leads to regeneration of villi, but in some patients these infections are prolonged so the destruction of the jejenum mucous membrane is irreversible due to chronic diarrhea. IgA helps in elimination of pathogens from the surface of mucous membrane epithelial cells so the lack of this immunoglobulin may maintain infection by facilitating the binding of pathogens to the surface of epithelium [1, 2]. The prevalence of celiac disease in children with sIgAD and familiar occurrence of both diseases suggested a common genetic background of both diseases. Moreover, the haplotype of HLA: A1, Cw7, B8, DR3, DQ2 is important for co-existence of IgAD and celiac disease [2, 6]. However, the precise analysis of frequency of celiac disease within the IgAD population does not support this hypothesis because the co-existence of celiac disease and sIgAD is lower than expected based on the effect of a common genetic background. Another hypothesis of association of celiac disease and IgAD proposes an increase of B lymphocyte stimulating factors (B-lymphocyte stimulator (BlyS) and a proliferation inducing ligand – APRIL) noted in IgAD patients as an important factor. A new, large, in-depth study did not reveal differences between the level of these factors in IgAD with or without concomitant celiac disease [7]. It seemed, that the possibility of destruction of the mucous membrane and occurrence of clinical symptoms due to disturbed metabolism of gliadin in the case of a lack of secretory IgA is more probable [2]. In the histology of biopsy in celiac disease the pattern of changes in the jejenum is similar in patients with or without IgAD. A gluten-free diet (GFD) is effective, despite sIgAD.

The frequency of Crohn’s disease and ulcerative colitis in people with IgAD is unknown [2, 8–11]. Moreover, in adults with IgAD, nodular lymphoid hyperplasia (NLH) is described as a separate clinical entity. The high amounts of large nodules consisting of B lymphocytes producing mainly IgM, located along mucous membrane of the gastrointestinal tract, lead to symptoms of malabsorption, flattening of villi, and even jejenum occlusion [2]. The differential diagnosis of inflammatory/autoimmune disease of GI in sIgAD patients is very difficult because of overlapping of clinical symptoms and similar changes in histology of jejenum biopsy.

Common variable immunodeficiency

Common variable immunodeficiency (CVID) was primarily described in adults, so the majority of data about the clinical symptoms and course, clinical symptoms in concomitant diseases, are based on observations from adult patients. The frequency of CVID is between 1 : 25000 and 1 : 50000. Diagnosis is based on exclusion of known causes of noted clinical symptoms and hypogammaglobulinemia. Criteria of CVID are lower level of IgG only or IgG and a second immunoglobulin (IgA or IgM), low level of specific antibodies to vaccination antigens, and disorders in cellular immunity in marked percentage of patients. A lower number of T lymphocytes, adverse proportion between CD4 and CD8 subpopulations, and low proliferation indexes after mitogen and antigen stimulation are observed [1, 2, 11–13]. Clinical symptoms of CVID are different in children and adults [14]. In patients diagnosed as adults chronic sinusitis, bronchiectasis, and chronic lung disease are often observed, while in children diagnosed with CVID these symptoms are very rare. Measurement of immunoglobulin levels in children is due to frequent infections of the respiratory tract, otitis, sinusitis (in older children) char-
characterized by prolonged course, and weak response to antibiotics. Low levels of immunoglobulins (according to age-related level) and no increase in response to infection are the basis of humoral immunodeficiency diagnosis—common variable immunodeficiency (CVID).

Autoimmune diseases occurred in 20–30% of CVID patients as hematological symptoms, mainly thrombocytopenia, leukopenia, and neutropenia [9, 15]. After hematological symptoms, autoimmune and chronic inflammatory diseases of the gastrointestinal tract, e.g. Crohn’s disease, celiac disease, atrophic gastritis with megaloblastic anemia, autoimmune hepatitis, ulcerative colitis and nodular lymphoid hyperplasia (NLH), are noted in these patients [2, 5, 11, 16, 17]. This sequence of autoimmune diseases in CVID (first—haematological symptoms, second—GI tract, other—less frequent) is based on data from adult patients. There are a few observations from children about co-existence of autoimmunity and CVID. Thrombocytopenia, neutropenia, hemolytic anemia and gastrointestinal tract disease (inflammatory bowel disease—IBD, celiac disease) are frequent in children but the proportions between them and frequency of particular diseases are not known. Autoimmunity of the gastrointestinal tract in children with CVID is second in frequency after hematologic symptoms, like in adults. However, in children with CVID celiac disease, Crohn’s disease and hepatitis are common while in adults rheumatoid arthritis, skin diseases, systemic lupus erythematosus, primary biliary cirrhosis, pernicious anemia, and atrophic gastritis are more frequent [2]. The diagnosis of autoimmune disease includes clinical symptoms and circulating antibodies for described cellular and tissue antigens. In CVID the serological diagnosis is problematic because of 2 reasons: first, low production of specific antibodies typical for humoral immunodeficiency; and second, lack of gA in IgAD and in some CVID patients. In autoimmune/inflammatory disease of the GI tract antibodies in IgA class were clinically significant as a consequence of IgA’s role in GI mucous membranes. Considering the results of antibody detection as significant for diagnosis in IgA class only, in the case of CVID patients may lead to false negative results. Now, tests detecting antibodies are performed in both (IgA and IgG) classes of immunoglobulins as routine. Moreover, the histology of the jejunum in IBD in patients with IgAD and CVID shows some differences as compared to IBD histology in patients without immunodeficiency. It seems that disturbances in B lymphocyte ontogeny in CVID, e.g. abnormal process of maturation, incomplete hypermutation, lack or low number of B memory cells, are associated with a different pattern of histology of tissues involved in the autoimmune process [2, 17, 18]. In jejunum biopsy from patients with CVID and celiac disease or Crohn’s disease the number of B lymphocytes in the infiltration is low, and plasmocytes are singular or absent. This different histology is so typical and characteristic for CVID patients that these diseases are called celiac-like disease and Crohn’s-like disease to discriminate between patients with or without immunodeficiency [2].

**Deficiency of specific antibody synthesis**

In this deficiency the level of immunoglobulin is within the normal range but the clinical course of infections suggests a deficiency. The most common infections such as tonsillitis, pharyngitis, and bronchitis become severe, almost septic in otherwise healthy children. Levels of IgG and subclasses of IgG are within the normal range, and parameters of cellular immunity are without disorders. The immunodeficiency is diagnosed based on the low level of specific antibodies to vaccination antigens only [2, 9]. The low level of specific antibodies suggests disorders of their production and is the main symptom of this immunodeficiency. Similar to CVID, this type of immunodeficiency is an indication for regular immunoglobulins’ substitution [12].

**Immunoglobulins’ substitution**

The regular substitution of immunoglobulins in a dose of 0.4–0.5 g/kg b.w/month intravenously or subcutaneously delivers the specific antibodies to common pathogens. Decrease in frequency and milder clinical course of infections are the main goals to obtain with immunoglobulins’ substitution. In the case of IBD in CVID the regular substitution is effective in prophylaxis of infections but has no influence on the course of concomitant autoimmune/inflammatory GI disease. One plausible explanation indicated lack of possibility to reach the epithelial jejunal surface by immunoglobulin molecules [2]. However, in other autoimmune diseases co-existing with CVID, e.g. chronic thrombocytopenia or neutropenia, regular substitution increased the number of platelets or neutrophils in CVID patients, although the low dose of IgG is below the proved suppressive effect on the autoimmune process [2]. It might be the effect of anti-inflammatory activity of IgG, even in a prophylactic dose. The suppressive effect of immunoglobulin infusion is associated with a high dose (1.0–2.0 g/kg b.w/therapy). This high-dose therapy is recommended in acute thrombocytopenia (e.g. associated with viral infection), Kawasaki disease, chronic polyneuropathy with demyelination, hemolytic anemia and others [12].
Diagnosis of gastrointestinal tract autoimmune diseases

Standards of autoimmunity of GI diagnostic procedures

The standard diagnosis of GI autoimmunity is performed in people with clinical symptoms and consists of laboratory tests (detection of autoantibodies), imaging procedures (gastroscopy, colonoscopy and other radiological methods) and histology of jejunal mucous membrane biopsy [19–21]. The laboratory markers are helpful in early diagnosis preceding the onset of severe clinical symptoms in many patients. In recent years, the detection of antibodies associated with the GI autoimmune process is commonly used for screening in the risk group of children including humoral immunodeficiencies (IgAD, CVID).

Antibodies

Celiac disease

Typical clinical symptoms for celiac disease are observed in about 20% of patients (classic form of disease) [22]. In the remaining patients, clinical symptoms suggest jejunal dysfunction and malabsorption syndrome leading to hypochromic anaemia, occurrence of aphthae and aphthous stomatitis, osteopenia, sometimes osteoporosis with bone fractures, low level of iron resistant to oral therapy, and hypoproteinaemia. These symptoms are not directly associated with the gastrointestinal tract. Diagnosis of latent, silent or atypical form of celiac disease, often in older children, teenagers and adults, is based on complex procedures. The genetic background of celiac disease is associated with expression of HLA-DQ2 and HLA-DQ8 determinants, which explains the familiar predisposition to this disease. Commonly used antibodies tested during diagnostic procedures for celiac disease include antibodies against gliadin, tissue transglutaminase and endomysium. Antibodies in IgA class are clinically significant, but for people with IgAD or CVID without IgA, antibodies in IgG class are significant. Specificity of ASCA antibodies is estimated as 99%, sensitivity as 79%.

Indirect fluorescence is used for detection of antibodies against exocrine pancreas tissue (PAB) and product of pancreatic cells (drop like fluorescence). Antibodies in IgA class are clinically significant, but for people with IgAD or CVID without IgA, antibodies in IgG class are significant. Specificity of ASCA antibodies is estimated as 99%, sensitivity as 79%.

Ulcerative colitis

The detection of antibodies in serological diagnosis of ulcerative colitis (UC) has been used for a few years. Antibodies against mucin produced by goblet cells (GAB), against neutrophil myeloperoxidase (ANCA) and antinuclear (ANA) are assayed with indirect immunofluorescence or ELISA. The GAB are noted in about 80% of patients with UC.

Jejunum histology

In celiac disease changes in the jejunum are classified according to the Marsh, Oberhuber and Corazza scale [24]. The most common Marsh scale includes the number of intraepithelial lymphocytes (IEL), proportion of crypt number and villi height, and structure and height of villi. Patients with clinical symptoms and a positive serological test but without changes in jejunum villi parameters are problematic (Marsh scale 0) [27]. In these patients the electron microscopy seemed to be a resolution and changes seen at microscopic level are diagnosed as microscopic enteritis [28, 29].

The typical pattern in chronic inflammatory bowel disease consisted of infiltration, development of new...
lymphoid nodules, and increase of IEL number. In celiac disease the infiltrations consist of T and B lymphocytes, plasmocytes and a few monocytes. Interesting was the high percentage of TCR γδ lymphocytes within T lymphocytes infiltrating the submucous level of the jejunum wall. The high number of TCR γδ was higher when celiac disease occurred in IgAD patients [30]. In celiac disease infiltrations are free from neutrophils often noted in infiltrations typical for Crohn’s disease and UC. Presence of given cell populations within infiltrations is associated with different profiles of cytokines, mainly proinflammatory, produced locally. Production of antibodies by B cells present in infiltrations is induced by antigens present in close contact with immunocompetent cells, e.g. neutrophils dying in situ, which leads to production of ANA and ANCA [20, 21].

**Celiac disease in immunodeficiency**

Diagnosis of celiac disease in humoral immunodeficiency is difficult because of scanty and unspecific symptoms and because of overlapping of these symptoms, e.g. periodic or prolonged diarrhea, and abdominal pain caused by IgAD only, without concomitant celiac disease [31, 32]. In children without immunodeficiency anti-endomysial antibodies, antibodies to gliadin and tissue transglutaminase are produced mainly in IgA class (immunoglobulin of mucous membrane). These same antibodies are produced in IgAD patients but in IgG class. In patients with CVID, the problem of antibody production is more complex due to IgA deficiency in a marked number of patients and weak production of antibodies in response to antigens including autoantigens. However, permanent presence of autoantigens in contact with immunocompetent cells may be strong enough for induction of antibody production, despite weaker function of the immune system. The level of these antibodies is above the limit of a positive value, but lower than observed in children without immunodeficiency.

Standard diagnostic procedures in celiac disease consisted of serological tests detecting typical antibodies in serum in patients with clinical symptoms suggesting celiac disease and histology of jejunum biopsy. In some patients, despite typical clinical symptoms, the histology of the jejunum is negative [22, 27]. Submicroscopic study helps in individual cases showing very delicate but typical changes [29]. Following this, clinicians suggest GFD when the clinical symptoms are present without histological proof of celiac disease in typical analysis of biopsy. Moreover, the submicroscopic changes are also an indication for GFD [29].

Observations of GFD effects in patients with CVID showed resistance to this therapy in about 20% of patients. Within this group of CVID patients lack or very low level of IgA was frequent. Jejunum dysfunction and malabsorption syndrome progress despite restricted GFD, leading to inhibition of growth and development of malnutrition.

**Crohn’s disease and UC in immunodeficiency**

Adults with CVID and gastrointestinal involvement demonstrate chronic diarrhea in about 10% to 50% of patients [2, 8, 12, 16, 18]. In children with IgAD, CVID diarrhea is less frequent but studied groups were small. The bowel inflammatory disease in immunodeficient patients demonstrated different histology often compared to lymphocytic colitis than typical Crohn’s disease or UC [2]. Regular substitution of immunoglobulins does not inhibit progress of inflammation, and does not help in regeneration and healing of mucous membrane damage. Hypotheses explaining the lack of effects of immunoglobulins’ substitution are various, including defect of regulatory T lymphocytes (Treg CD4/CD25/FoxP3), effects of different profiles of proinflammatory cytokines produced locally and, what seemed to be most interesting, lack of possibility to reach the surface of the epithelium by immunoglobulins given intravenously. This phenomenon is important in patients with CVID and a low level or lack of IgA [2].

In histology of jejunum from patients with CVID and IBD, the cellular infiltrations consisted mainly of T lymphocytes with a low number of B lymphocytes and few or no plasmocytes [2, 12]. Diagnosis of UC is often difficult in patients without immunodeficiency so this diagnosis in patients with CVID is much more problematic. In a study including 248 patients (children and adults) with CVID, UC was noted only in 7 patients. However, in 10 other patients demonstrating clinical symptoms of inflammation the final diagnosis was not established. It showed the difficulties in differential diagnosis of jejunum diseases in immunodeficient patients [11].

**Differential diagnosis – “collagenous sprue”, microscopic and autoimmune, chronic bowel inflammation**

Collagenous sprue (CS) is a rare, severe disorder of jejunal function (absorption process mainly) with a low number of crypts, flattening of villi, and collagen deposits under the epithelial cell layer containing cellular elements within. This histology is typical for diagnosis of CS [33]. However, similar symptoms, e.g. histology with flattening of villi, lack of response to GFD (observation during at least 1 year), are noted in refractory celiac disease (RCD), which might suggest wrong diagnosis and delay in CS diagnosis. Precise diagnosis is very important as CS is a progressive disease leading to severe malabsorption syndrome, cachexia and death. Therapy
is based on steroids, immunosuppression and total para-
etal nutrition [32]. Up to now this disease has been not-
eted in patients without immunodeficiency, although CS
symptoms overlapping diet refractory celiac disease
with cachexia may suggest CS in these patients.

Autoimmune enteropathy (AE) was separated as
a new entity in young children with chronic diarrhea and
antibodies to epithelial cells (anti-enterocyte antibodies)
as a marker of the autoimmune process. The first case
was described in a child with IgAD, which suggests the
association between AE and immunodeficiency. The
majority of patients were boys diagnosed in the first
year of life [28]. Anti-enterocyte antibodies seemed to
be important for induction and supporting the process
of jejunum mucous damage but it has not been proved
yet. However, in other prolonged inflammatory diseases,
e.g. Crohn’s, celiac disease or UC, these antibodies are
absent, supporting the idea of a separate diagnostic and
clinical entity [28].

Microscopic enteritis (ME) was used first in adults
showing malabsorption symptoms without inflammation
characteristics, without changes in vill structure or ulcers
present in light microscopy [29]. Such enteritis might
explain symptomatic celiac disease without changes in
jejunum mucous (Marsh scale 0) due to overlapping
symptoms [24, 27, 29]. Differentiation between these two
syndromes is possible with electron microscope assay.
Submicroscopic changes are more typical for celiac dis-
cease with minimal mucous damage (Marsh 0).

Algorithm of differential diagnosis
in children with immunodeficiency

Children with immunodeficiency and gastrointestinal
tract involvement demonstrate abdominal pain, me-
trism, feelings of discomfort, lack of appetite, periodic
diarrhea or constipation. In other children without gastric
symptoms the inhibition of growth and underweight are
noted, suggesting discrete malfunction of the jejunum.
High prevalence of gastrointestinal autoimmune dis-
esses in this group of children is an indication for
a screening test of typical autoantibodies in serum.
Observations of preserved autoantibodies’ production in
immunodeficiency such as CVID and IgAD modify the
common view about the possibility of the immune sys-
tem to respond to antigens. Studies of antibody pro-
duction are focused on vaccination antigens given 2
or 3 times in a single dose in precise periods of time.
The low function of memory in CVID or disorders of specific
antibody synthesis resulted in low titers of specific anti-
bodies. In the autoimmune process, aautoantigen is pres-
ent permanently in contact with immunocompetent
cells, stimulating them effectively to production of anti-
bodies. The final level of antibodies in serum is often low-
er than in children without immunodeficiency. In conse-
quence of this the limit of a positive result should be
lowered. Considering low levels of antibodies as positive
results, children with a probable autoimmune process are
selected for further tests, repeating the antibody assay
after 4–6 months, with careful clinical observations,
undertaking diagnostic procedures without delay [34].
Presence of antibodies, even at low levels, and discrete,
unspecific clinical symptoms are indications for a diag-
nostic procedure including histology of jejunum biopsy
without repeating the antibody assay.

In celiac disease diagnosed in children with IgAD,
restricted GFD is effective as in children without IgAD. In
CVID the response to GFD in the majority of patients is
good but in about 20% of patients resistance to GFD
and progress of symptoms are noted. The course of dis-
eease in these patients is severe, and time to obtain
remission is longer. Therapy with steroids, monoclonal
antibodies against TNF and immunosuppression might
be effective.

Crohn’s disease is more frequent than UC in children
with immunodeficiency. Unusual clinical course results
in delay of diagnostic procedures. Antibodies detected
before severe clinical symptoms signal the autoimmune
process and, in consequence, introduction of therapy
which diminishes the development of malabsorption
syndrome and jejunum damage. Regular substitution of
immunoglobulins in CVID prevents infections and pro-
tects patients during steroid or immunosuppressive
therapy for Crohn’s disease or UC.

Our observations

Detection of antibodies typical for Crohn’s disease
and celiac disease was performed in 43 children diag-
nosed with CVID and 63 children with IgAD. Antibodies
typical for celiac disease (against endomysium tissue
transglutaminase and gliadin) were noted in 14 children
(3 diagnosed with CVID, 11 with IgAD). Two of them were
diagnosed as celiac despite weak and unspecific clinical
symptoms. Antibodies typical for Crohn’s disease were
noted in 16 children (7 diagnosed with CVID, 9 with
IgAD). The titer of antibodies was close to 20 units (bor-
der level for a positive result) but because of immuno-
ecficiency was considered as positive followed with clin-
icl care ful observations and monitoring antibodies
every 4–6 months.

Based on our observations and results of the study
we suggest that in patients with immunodeficiency and
gastrointestinal symptoms indicating an autoimmune or
inflammatory process, the diagnostic procedures and
therapy may need modifications of general standard
methods and working out new standards.
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