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REVIEW ARTICLE

Autoimmune enteropathy in children and adults

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Abstract

Autoimmune enteropathy is a rare disorder characterized by severe and protracted diarrhea, weight loss from malabsorption and immune-mediated damage to the intestinal mucosa, generally occurring in infants and young children, although some cases of adult onset have been reported in the literature. Pathogenetic mechanisms involve immunological disorders, in which the presence of antienterocyte autoantibodies, although detected since first description, seems now to be secondary. As occurs frequently in autoimmunity, subjects with autoimmune enteropathy may be affected by other autoimmune disorders, sometimes leading to particular forms, i.e. the IPEX syndrome and the APECED syndrome. The prognosis of autoimmune enteropathy patients depends on the severity of digestive symptoms (including fecal output), on the severity and extension of histological lesions along the gastrointestinal apparatus, and on the presence of extra-intestinal involvement. Management of autoimmune enteropathy patients is based on nutritional support and adequate hydration to ensure optimal growth and development, together with immunosuppressive therapy. Recently, biological agents have been introduced, with apparent beneficial effects.

Key Words: *APECED syndrome, autoimmune enteropathy, differential diagnosis, IPEX syndrome, protracted diarrhea*

Introduction

Autoimmune enteropathy (AE) is a rare disorder characterized by severe and protracted diarrhea, weight loss from malabsorption and immune-mediated damage to the intestinal mucosa, generally occurring in infants and young children, although some cases of adult onset have been reported in a number of studies [1–8]. The disorder was described for the first time in 1982 by Walker-Smith et al. in a male child [9]. Nevertheless, a role of autoimmunity in the pathogenesis of the protracted diarrhea of infancy had been previously hypothesized in 1978 by McCarthy et al.; they described the case of an adolescent boy with immunoglobulin A deficiency and autoantibodies binding to cytoplasm of the villous epithelial cells, in which the clinical picture, characterized by diarrhea and weight loss, regressed only after immunosuppressive therapy [10]. Moreover, in the same years some investigators described familial syndromes of intractable diarrhea in infants in which the presence of autoimmune diseases (diabetes mellitus, thyroiditis, hemolytic anemia) supported the hypothesis that an immunologic disorder could also be involved in the pathogenesis of the intestinal picture [11,12].

Epidemiological data

Between 1993 and 1996, a 3-year prospective multicenter survey on severe and protracted diarrhea in pediatric patients was carried out by the Italian Society of Pediatric Gastroenterology and Hepatology; this survey indicates that severe and protracted diarrhea syndrome is a rare disorder in Italy, affecting less than 1 out of 100,000 infants each year, with AE representing the most frequent diagnosis, with a prevalence of 25% [13]. Similar results were found in an earlier multicenter European survey, in which 29% of children with intractable diarrhea fulfilled the diagnostic criteria of AE [14].

In adult subjects, there is less epidemiological data, but it seems that this condition is even more

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rare, only a few cases being reported in the literature [1–8].

Pathophysiology

In recent years, the immunologic mechanisms causing AE have been widely debated. It is known that enterocytes are crucial in directing the appropriate immune response to luminal antigens; in fact, intestinal epithelium is an interface between environmental and food antigens and cells of the mucosal immune system. The constitutive expression of human leukocyte antigen (HLA) class II molecules on the enterocyte surface is another significant feature of this intestinal barrier, because epithelium cells are known to present processed exogenous antigenic peptides to the clonotypic T-cell receptor, in order to maintain the oral tolerance [15–17]. It has been shown that, in the context of autoimmunity, the expression of self-antigens on the epithelial cell surface can activate CD4 T lymphocytes: this phenomenon, described in classic autoimmune diseases such as insulin-dependent diabetes mellitus and autoimmune thyroid disorders, may play an important role in the destruction of epithelial cells [18,19]. Supporting the possible role of these mechanisms also in the pathogenesis of AE, Mirakian et al. documented the inappropriate expression of HLA class II molecules in the crypt epithelium of proximal small intestine in children affected by AE [20]. Moreover, Cuenod et al. described an increase of mucosal T lymphocytes and overexpression of HLA-DR antigens by enterocytes, suggesting that the gut is the site of an autoimmune reaction mediated by local activation of intestinal autoreactive T cells, causing typical histologic lesions of AE [21]. In subjects affected by AE, increased levels of CD4 and CD8 T lymphocytes in the lamina propria and intraepithelial presence of CD8 T lymphocytes have been reported in some studies [22–24]. Intestinal T lymphocytes could act through different mechanisms, by exerting direct cytotoxicity against epithelial cells, or causing enterocyte apoptosis with an antibody-dependent cellular cytotoxicity, or through the secretion of lymphokines [25–28]. Moreover, it is known that the activation of CD4 T lymphocytes against self-antigens may also be due to thymic dysfunction. In fact, intrathymic T-lymphocyte maturation is important for the deletion of potentially self-reactive clones of T cells [29]; when this process is altered, autoreactive T-cell clones may induce the expansion of anti-self B cells [30]. The role of T-cell activation in the pathogenesis of AE is confirmed by the efficacy of treatment with cyclosporin A, a drug that acts by suspending certain nuclear events associated with T-cell activation [31–35].

Regarding antienterocyte autoantibodies, they have been detected since the first description of AE [9]. Immunohistological studies of serum from patients affected by AE have shown that these autoantibodies, frequently of IgG type, can be directed against intestinal brush border or cytoplasm of enterocytes; also goblet cells can be targeted [22,36,37]. It seems that their role in AE pathogenesis is secondary, since these autoantibodies seem to appear only after the onset of mucosal damage, disappearing after treatment even if a complete return to normal mucosa has not yet been achieved; moreover it seems that there is no correlation between their titers and the histological severity of the enteropathy [9,38–40]. In addition, their presence is not pathognomonic, considering that antibodies to enterocyte components at low titers have also been found in patients affected by other gastrointestinal disorders, such as inflammatory bowel disease and cow's milk allergy, and in adults with HIV infection [36,41,42].

As occurs frequently in autoimmunity, subjects with AE may be affected by other autoimmune disorders; in this regard, several autoantibodies (e.g. antibodies towards gastric parietal cells, pancreatic islets, insulin, glutamic acid decarboxylase, smooth-muscle, endoplasmic reticulum, reticulin, gliadin, adrenal cells, nuclear antigens, DNA, thyroglobulin and thyroid microsomes) have been described in AE, some of these acting against common antigens [1,43]. Among these, a recent extensively studied antibody is the one directed against a 75 KDa antigen located in gut and kidney epithelia [37,44]. This antigen, named AE 75, was identified by Kobayashi et al. in two Japanese patients; his genomic sequence is located on the chromosome 11p14.3 [37]. The protein encoded by AE 75 participates in interactions between membrane-associated proteins and other cytoplasmic proteins involved in cytoskeletal arrangement, in tight junction formation and in the regulation of paracellular enterocyte permeability [37,45,46]. Therefore, autoantibodies to AE 75 may impair the tight junction integrity, thus inducing enhanced intestinal permeability and, finally, inflammatory enteropathy [46]. Considering that the presence of AE 75 was detected in duodenal, jejunal, ileal and renal tissues of these patients, also complaining of renal disorders, the investigators hypothesized that AE 75 could be a common target of tissue damage in both organs [37]. Colletti et al. reported a case of AE complicated with immune-mediated membranous glomerulonephritis, in which autoantibodies reacted with a 55 kD antigen located in both the jejunum and glomerulus; also in this case, the epitope is located on the epithelial cells of both the small intestine and kidney [47].

A particular form of AE associated with other autoimmune diseases is represented by the IPEX syndrome, so named for its peculiar X-linked transmission. It was first described by Powell et al. by observing death from severe and protracted diarrhea in 8 of 17 male subjects with polyendocrinopathy and various autoimmune disorders in the same family over three generations [12]. In the human being, genetic mapping studies have identified the IPEX locus to chromosome Xp11.23-q13.3 [48–50]; the gene was named FOXP3, and encodes a 48 KDa protein named scurfin [50]. This protein is predominantly expressed in CD4+/CD25+ T cells, a subpopulation characterized by regulatory functions on T-cell activation (T-reg cells) [48–51]. Several mutations have been described, causing loss of regulatory funtions of T-reg cells and subsequent activation of immunitary reactions [52–54]. The IPEX syndrome has been described only in males, whereas females are asymptomatic carriers; this has been demonstrated in a study by Tommasini et al., in which peripheral blood lymphocytes from a healthy heterozygous female expressed only one single FOXP3 transcript, either wild-type or diseased, suggesting the X-inactivation for this gene [55]. Another particular familial syndrome including AE is the APECED syndrome that shows autoimmune phenomena, polyendocrinopathy, candidiasis, and ectodermal dystrophy. Also known as autoimmune polyglandular syndrome 1 (APS-1), the APECED syndrome is one of the rare monogenic autoimmune diseases, with an autosomal recessive inheritance and no association to HLA. The gene responsible, designated AIRE (autoimmune regulator), has been mapped to the chromosome 21q22.3, and encodes for a protein implicated in the regulation of gene transcription. In particular, this protein is involved in architectural organization of the thymic microenvironment, leading to normal processes of T-cell intrathymic negative selection; genetic disorders of the coding region of AIRE cause the loss of function of this protein, with consequent development of autoreactive T cells [56].

Intestinal morphology

The histopathology of AE has some analogies with celiac disease, with duodenal and proximal jejunum biopsies showing total villus atrophy, crypt hyperplasia, and a dense lymphoplasmacytic infiltrate into the lamina propria; crypt abscesses are found in the most severe cases. Unlike celiac disease, there is a relative paucity of intraepithelial lymphocytes, expressing the T-cell receptor αβ [5]. At immunohistochemistry, crypt enterocytes show hyperexpression of HLA class II molecules, whereas lymphocytic infiltration of intestinal mucosa is constitued by CD4-CD8 T lymphocytes and macrophages [21–24].

In both children and adults affected by AE, the presence of lesions in both the stomach and colon has been described, supporting a possible generalized autoimmune disorder involving the whole gastrointestinal tract in these patients. Gastric biopsies showed dense lymphoplasmacytic infiltrates, predominantly composed of CD4+ T lymphocytes, located in the lamina propria, leading up to marked atrophic gastritis with intestinal metaplasia, as well as glandular destruction [8]. Morphological lesions in the colon varied from diffuse mild colitis with only an increase in inflammatory cells (lymphocytes, plasma cells, and a discrete presence of eosinophils) to severe colitis with goblet-cell depletion, crypt dysplasia, distortion of crypt architecture, and crypt abscess formation. Immunohistochemistry shows features similar to those found in the small intestine [8].

Clinical features

The clinical picture of AE is ridden by severe and protracted hypersecretory diarrhea, generally occurring in the first weeks of life and, typically, requiring parenteral nutrition to ensure the hydroelectrolytic balance. The intestinal malabsorption leads to low body-weight and low growth [13]. Moreover, patients affected by AE often suffer from local and systemic infections, because of loss of skin and gut barriers, central lines, immunosuppressive therapies, and poor nutrition [57].

The prognosis of AE patients depends on the severity of digestive symptoms and signs (including fecal output), on the severity and extension of histological lesions along the gastrointestinal apparatus, and on the presence of extra-intestinal involvement [21,58]. In fact, AE could be one manifestation of a more diffuse autoimmune disorder of the gastrointestinal system, characterized by gastritis, colitis, pancreatitis, and hepatitis, with a variety of autoantibodies, such anti-parietal cell antibodies and anti-goblet-cell antibodies [4,8,57]. Leòn et al. described the association of AE and autoimmune colitis as "generalized autoimmune gut disorder" [5]. Pancreatic involvement, usually arising in the form of autoimmune diabetes mellitus, may also precede the onset of secretory diarrhea in infants; other pancreatic diseases occurring in AE are represented by chronic pancreatitis, with lymphocytic infiltration and atrophy of exocrine parenchyma. Liver can show hepatocellular necrosis, up to chronic hepatitis and hepatic fibrosis; another form of chronic liver involvement is constitued by autoimmune hepatitis, with positivity of smooth muscle autoantibodies [59].

As mentioned above, during the course of the disease, also other extra-intestinal organs can be involved. In particular, the thyroid may show lymphocytic infiltration and interstitial fibrosis with onset of hypothyroidism; kidney may be involved in the form of interstitial nephritis or membranous glomerulonephritis, but also with hematuria and proteinuria, up to nephrotic syndrome [57]. Hematologic disorders, like hemolytic anemia and thrombocytopenia, have been reported, with Coombs' test positivity. Lung and skin involvement may occur in the form of interstitial pneumopathy or bronchitis and eczematiforme dermatitis [57,59]. Volta et al. have also described a case of an association between AE and rheumathoid arthritis [60]. Thus, AE is frequently a multivisceral disorder, in which intestinal involvement may be the initial manifestation of disease, generally in the first months of life [36].

On the basis of the above-mentioned role of the thymus in the deletion of potentially self-reactive clones of T cells, an association between thymoma and the development of autoimmunity has been hypothesized; in this regard, some cases of AE have been reported in the setting of thymoma, in both pediatric and adult age [2,61].

In the context of the IPEX syndrome, a severe form of AE occurs in association with polyendocrinopathies (in particular, type 1 diabetes mellitus) and skin manifestations (e.g. eczema, psoriasis, atopic dermatitis, alopecia). As occurs also in the classic form of AE, other disorders may arise during the natural history of the IPEX syndrome, owing to immune dysfunctions: production of autoantibodies, Coombs-positive anemia, autoimmune cytopenias, lymphadenopathy, splenomegaly, thymic involution, pneumonitis, nephritis, hepatitis, arthritis, myositis, and fatal infections [12,62,63]. All these diseases often appear sequentially, rather than simultaneously, and the organ spectrum can vary from patient to patient. Survival is influenced by several factors, such as genotype, environment, and treatment strategy, but the majority of patients die in infancy or childhood [64].

In the APECED syndrome, AE is associated with variable endocrine deficiencies, chronic mucocutaneous candidiasis, and ectodermal dystrophy. This syndrome is more frequent among some isolated populations, such as Finns, Sardinians, and Iranian Jews [65]. The first sign is frequently a chronic mucocutaneous candidiasis, starting soon after birth, affecting the tongue, esophagus, and nails; several cases of oral carcinoma being reported in literature, it has been suggested that it might be carcinogenic [66]. Candidiasis is followed by autoimmune hypoparathyroidism or Addison's disease, often in the first decade of life. Several autoimmune disorders such as autoimmune gastritis with pernicious anemia, autoimmune hepatitis, type 1 diabetes mellitus, autoimmune thyroid disease, and gonadal dysfunction can arise. Moreover, the patients may develop alopecia with patchy or complete loss of hair, vitiligo, urticaria-like erythema, keratoconjuctivitis, and ectodermal dystrophies affecting enamel and nails [56].

In adult age, only a few cases of AE have been described in the literature [1–8]. Corazza et al. reported on four adult women affected by celiac disease who were not responsive to a gluten-free diet; in two of these cases, the diagnostic criteria proposed by Unsworth & Walker-Smith were fulfilled for diagnosis of AE: these patients had no malabsorption symptoms in childhood, so confirming an adult onset [1]. As in pediatric patients, also in adult age, some investigators have reported the association of AE with gastritis and colitis, suggesting the existence of a generalized autoimmune disorder of the alimentary tract; moreover, AE is frequently found in adults affected by other autoimmune diseases, or predisposed to autoimmune diseases (positivity for organ-specific and/or non-organ-specific autoantibodies), or with a familial history of autoimmunity [4,5,8]. The onset of AE in adult age can occur also in the context of the IPEX syndrome [67].

Diagnosis

AE should be taken into account in all patients presenting with severe diarrhea requiring parenteral nutrition, particularly in infants, being considered the most common cause of protracted diarrhea of infancy [13].

In the diagnostic work-up of these patients, it is important to evaluate birth and family history, timing of onset of diarrhea, and possible triggers, such as viral diseases in the family and introduction of new foods. Furthermore, the type of diarrhea should be considered, because secretory diarrhea that characterizes AE is usually not responsive to bowel rest. Small-bowel biopsy is a cornerstone of investigation, and if it shows intestinal villous atrophy and inflammatory infiltration with hyperplastic crypts, AE should be considered in the differential diagnosis, like other disorders characterized by similar histologic findings (cow's milk intolerance, celiac disease, parasitic infestations, bacterial and viral infections, and intestinal lymphoma) [57]. Considering its many similarities with autoimmune enteropathy, special mention should be given to celiac disease regarding not only the histological pattern, but also the gut clinical setting, as well as the possible association with other autoimmune diseases; however, in the subset of patients with a

diagnosis of celiac disease without specific antibodies, the lack of response to a gluten-free diet should suggest not only a condition of refractory celiac disease, but also a case of AE. Furthermore, endoscopic examination of the colon is mandatory to complete an adequate differential diagnosis.

The diagnostic criteria to make a correct diagnosis of AE, originally proposed by Unsworth & Walker-Smith et al., are: a) protracted diarrhea and severe enteropathy with small-intestinal villous atrophy; b) no response to exclusion diets; c) evidence of predisposition to autoimmune disease (presence of circulating enterocyte antibodies or associated autoimmune disease); and d) no severe immunodeficiency [43].

B- and T cells, lymphocytic subsets and polymorphonuclear cell counts are generally normal, as also are lymphocyte stimulation assays, serum immune complex, and complement factor levels [59]. IgA deficiency has been described with high incidence in autoimmune disorders, like AE, and it can be associated with villous atrophy [5,68].

A diagnosis of IPEX syndrome should be suspected in young male patients showing intractable diarrhea with villous atrophy and failure to thrive, associated with type 1 diabetes mellitus and/or hypothyroidism and with skin manifestations; this diagnosis is confirmed by mutation analysis of the FOXP3 gene [63].

The APECED syndrome should be hypothesized in patients with the above-mentioned clinical and ethnic features, in particular when these subjects are affected by at least two illnesses among chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism, and Addison's disease. Analysis of the AIRE gene mutation is recommended to confirm the diagnosis [56,65–66].

During follow-up, upper and lower endoscopy might be necessary in the case of gastrointestinal symptoms, in order to modulate or modify the therapy.

Management

AE patients need nutritional support and adequate hydration to ensure optimal growth and development. In the most severe cases, total parenteral nutrition must be started early, whereas where there is less severe involvement of the gut, an elemental or low carbohydrate-containing formula can promote enteral delivery of calories and nutrients, thus avoiding the complications of parenteral nutrition [69].

Immunosuppressive therapy, with corticosteroids, cyclosporin, tacrolimus, and mycophenolate mofetil, has been used with apparent benefit [31,61,70–73]. In particular, Sanderson et al. reported an improvement of small-intestinal mucosal morphology and carbohydrate absorption with a consequent more adequate growth in two children treated with cyclosporin A for 8 months [31]. In fact, cyclosporin A acts by suspending certain nuclear events associated with T-cell activation, which represents, as mentioned above, the crucial points in the pathogenesis of AE [31,35].

Recently, also in the context of AE therapy, biological agents have been introduced. In this regard, some cases of AE unresponsive to classic immunosuppressive therapy, in both pediatric and adult age, in which success has been achieved with infliximab treatment have been described [61,73]. This drug has been introduced because of its TNFα antagonistic effects, high levels of this cytokine being produced by intestinal intraepithelial T lymphocytes of AE subjects [61]. However, it should be remembered that these immunosuppressors carry an increased risk for infection, neurotoxicity, and lymphoproliferative disease [6]. Other resources are constitued by immunoglobulins, anti-lymphocytic immunoglobulin, or cyclophosphamide [70]. High doses of intravenous immunoglobulins block Fc receptors on cytotoxic T lymphocytes and natural killer (NK) cells, the effectors of antibody-dependent cytotoxicity [74]. The efficacy of high doses of cyclophosphamide was described by Oliva-Hemker et al. in an infant affected by severe AE unresponsive to other immunosuppressors such as methylprednisolone, cyclosporin A, tacrolimus, and 6-mercaptopurine [75]. The advantage of cyclophosphamide in a single treatment course is represented by its immunoablative but not myeloablative effects, because its metabolites are inactivated in hematopoietic stem cells but not in lymphoid cells; thus, T lymphocytes, B lymphocytes, and NK cells are rapidly eliminated by high doses of cyclophosphamide [76].

Regarding IPEX syndrome, it must be stated that this is a most severe form, which is often unresponsive to specific treatment, and is burdened with a high mortality rate (about 30%) [70]. As a first step, total parenteral nutrition is started, but it is often unsuccessful. Symptomatic treatment includes hematic transfusions and insulin for diabetes. Immunosuppressive therapy is the successive step [70–78]; among these drugs, recent data suggest that sirolimus is better tolerated, less nephrotoxic, and it allows T-reg cell expansion while the growth of effector T cells is inhibited [79]. Another option is bone marrow transplantation, but of patients so treated, none has survived long term [80]. A recent study suggests that, in the future, IPEX syndrome could be successfully treated with gene therapy of autologous cells; the direct transduction of T cells

with FOXP3-expressing vectors could overtake bone marrow gene therapy [81].

Also, the treatment of APECED syndrome is first of all based on parenteral nutritional support. The administration of corticosteroids in high intravenous doses, or immunosuppressors, particularly oral methotrexate, which is well tolerated in children, represents the successive step. Treatment should include hormone replacement and systemic chemotherapy against Candida infection. Patients should be followed-up and monitored for new disease components of the syndrome [56].

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