Intractable diarrhoea of infancy (Generic term)

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Intractable diarrhoea of infancy (IDI) was originally described by Avery et al. in 1968 as a syndrome characterised by diarrhoea occurring in a newborn younger than 3 months of age and lasting more than 2 weeks with three or more negative stool cultures for bacterial pathogens. Despite hospital treatment using intravenous fluids, the diarrhoea remained persistent and “intractable”. The mortality rate from infection or malnutrition was high and no specific diagnosis was obtained for most of the patients who died.

The term "IDI" was progressively used for older infants with severe and persistent diarrhoea despite adequate management. Such severe protracted diarrhoea resulted from associated factors, including increased intestinal permeability, food antigen sensitisation, bacterial overgrowth, infection and malnutrition, leading to a vicious pathological circle. Specific diseases were recognised and considered as “parenteral nutrition emerging diseases”. As it is clearly the parenteral nutrition that allowed progressively patients to survive, the term “severe diarrhoea requiring parenteral nutrition” was recently proposed. Two major subtypes can be differentiated within this group: i) “Protracted diarrhoea of infancy” (PDI) that may result from a sensitisation to a common food protein (e.g. cow’s milk), or may be secondary to a severe gastrointestinal infection (post-enteritis syndrome). PDI resolves despite its initial severity. ii) The second group is characterised by IDI. The term "intractable diarrhoea of infancy with persistent villous atrophy" is based on the histological observation of a flat intestinal mucosa and the clinical observation of diarrhoea starting within the first 2 years of life, which is abundant (>100 ml/kg/day) and persists despite bowel rest. Diarrhoea rapidly becomes life-threatening and long-term total parenteral nutrition is required. Diarrhoea sometimes persists for years despite prolonged bowel resting and various therapeutic trials.

The syndrome of IDI is heterogeneous and includes several diseases with different aetiologies. Provisional classification of IDI, according to villous atrophy and based on immunohistological criteria, was proposed by a group in Paris, France and currently accepted by the community. It distinguishes two clearly different groups of IDI:

1) Immune-mediated: characterised by a mononuclear cell infiltration of the lamina propria and considered as being related to T cell activation. Based on recent advances in the genetics of autoimmune enteropathy as well as the pathophysiology and clinical presentation, autoimmune enteropathy can be classified into three different types: the classical form of autoimmune enteropathy, identical to the so-called immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX) syndrome (autoimmune enteropathy type 1); autoimmune
2) The second histological pattern includes early onset severe intractable diarrhoea histologically characterised by villous atrophy with low or without mononuclear cell infiltration of the lamina propria but specific histological abnormalities involving the epithelium. Microvillus inclusion disease (MVID) and Intestinal epithelial dysplasia (IED), also known as tufting enteropathy, are congenital enteropathies presenting with villous atrophy and are thought to be related to abnormal enterocytes.

Another form of IDI that should be considered in a different way from the two other groups is so-called “phenotypic diarrhoea” or “syndromatic diarrhoea”. This form of IDI presents with severe early onset diarrhoea resisting bowel rest, non-specific villous atrophy and very characteristic extra-digestive (facial and hair dysmorphism) manifestations.

Clinically, IDI may be easy to diagnose on the basis of the symptoms onset, clinical presentation and associated disorders. Histopathological analysis confirms the diagnosis. It is crucial to distinguish IDI from PDI, since children with PDI always recover but infants with IDI remain dependent on parenteral nutrition for months, years and, in most cases, forever because of the permanent intestinal failure associated with the high rate of digestive loss. As long-term parenteral nutrition is associated with complications and/or poor quality of life, alternative treatments, such as intestinal transplantation, have to be considered.