EDITORIAL

Inflammatory Bowel Disease—Unclassified: How Much do we Know?

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Inflammatory bowel disease (IBD) is no longer a disease of the West as there are reports of increasing incidence of IBD in general, and Crohn's disease in particular, from India [1,2]. Though IBD is less common in children than in adults, almost one-fifth to a quarter of all cases are diagnosed in first two decades of life. There are three entities under the umbrella of IBD: ulcerative colitis (UC), Crohn's disease (CD) and IBD-unclassified (IBD-U). Proportion of these entities varies from country to country, and from region to region. In the West, around 60% of all cases of IBD in children are CD, 32% UC, and the remaining 8% IBD-U [3]. While in Northern India, UC is more common than CD, the reverse is true in Southern India [2]. Though there are set diagnostic criteria for CD and UC, IBD-U is basically a diagnosis of exclusion (cases of colonic phenotype of IBD that lacks features which will enable classification as CD or UC).

Understanding IBD-U assumes more importance in the pediatric population as the prevalence of IBD-U is higher among children than in adults (13% *vs.* 6%, respectively) [4]. The proportion of IBD-U declines with increasing age as evidenced by a large study of 1370 cases of IBD, where IBD-U (*n*=179) accounted for one-third of all IBD in children less than 2 years and the proportion dwindled to 9% in those above 13 years [5]. Clinically, this entity is indistinguishable from UC or CD with isolated colonic involvement. Nevertheless, the age of presentation is shown to be younger and disease severity is milder in IBD-U compared to UC or CD as evidenced by lower Physician Global Assessment scores (PGA), lower use of steroids, immunomodulators and colectomy rates in IBD-U [6]. The natural history suggests that IBD-U may be the early manifestation of either UC or CD in a proportion of cases. In EUROKIDS study, 38 of 117 (33%) cases of IBD-U were reclassified as UC (23, 60%) or CD (14, 37%) within median (IQR) 2.7 (1.0, 4.0) years of diagnosis [3]. Long-term follow-up studies in adults as well as in children have shown that almost half of the cases of IBD-U turned out to be non-IBD (non-specific colitis) [7,8]. Hence it is important to keep these patients on regular follow-up for reclassification (early) and to rule out IBD (in long run).

IBD is now diagnosed and classified according to the revised Porto criteria [9], which mandates ileocolonoscopy, esophagogastroduodenoscopy, histology and small bowel imaging in all cases (except for typical cases of UC). Though there is an exhaustive list of features to aid in classification of IBD, the picture gets complicated when ambiguity creeps in a case with colitis phenotype (thus labeled as IBD-U), like transmural inflammation without acute severe UC, macroscopic and microscopic rectal sparing, nonspecific inflammation and ulcers in upper gastrointestinal tract, ambivalent serological markers (pANCA, ASCA), reverse gradient of mucosal inflammation (more severe in proximal colon) and significant growth delay [9]. The importance of complete diagnostic work-up and strict adherence to the Porto criteria before labeling as IBD-U has been highlighted in a recent study that showed a reduction of prevalence from 7.7% to 5.6% on follow-up with complete re-investigation [3].

The study by Paul, *et al.* [10], published in this issue of *Indian Pediatrics*, is commendable in its effort to unveil the course of IBD-U in children. It emphasizes the importance of thorough work-up at diagnosis as per the revised Porto criteria, and also the readiness for repeat assessment and reclassification at follow-up. The inherent drawback of a retrospective study is obvious here as some information is missing. The detailed information about three cases that were later reclassified in another center was not available, and reasons for reclassification of these cases are unclear. In the present study [10], 40% were reclassified; of these, 70% were categorized as CD and 30% as UC, which is in contrast to previous studies. In the EUROKIDS registry (*n*=3, 461 IBD cases), 33% of IBD-U were reclassified out of which 60% were categorized as UC [3]. In another large pediatric IBD cohort (*n*=210), 50% of IBD-U were reclassified, within a median follow-up of 18.5 months, to UC (75%) or CD (25%) [11]. The long-term outcomes of

IBD-U in terms of treatment response, remission and requirement of surgery are not clear from the present study. More often remission is achieved and maintained in IBD-U with aminosalicylates alone, and the remission rate is higher than in CD or UC [6,7]. It has been suggested that aminosalicylates should be the first line of treatment in active IBD-U [6]. In light of the paucity of recommendations on treatment of IBD-U and exclusion of IBD-U from clinical trials on treatment strategies for IBD, there is a dire need to appraise treatment responsiveness and formulate evidence-based recommendations for IBD-U.

In view of the variations in prevalence, natural history, treatment response and a potential for reclassification of IBD-U, there is a need for further exclusive studies on IBD-U to better delineate this abstruse disease entity.

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