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REVIEW ARTICLE

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Back to the drawing board

Intestinal neuronal dysplasia type B: not a histological entity yet

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Introduction

Intestinal neuronal dysplasia of the submucous plexus (IND B) has been characterised by a group of clinical features indistinguishable from those of Hirschsprung's disease, including constipation, abdominal distension and enterocolitis [28]. The onset may be as early as the first few days of life and it has been commonly associated with Hirschsprung's disease, with which it has been associated with a worse outcome [27, 39]. It has also been associated with phaeochromocytoma, medullary carcinoma of the thyroid, carcinoid tumour, cystic fibrosis and paraneoplastic syndromes [8, 29, 40, 41].

The morphological features of IND B were first described by Nezelof et al. in 1970 [29] and clarified further by Meier-Ruge in 1971 [20], naming the condition as neuronic dysplasia of the colon. Continued research led to the description of the pathognomic features of IND B, which included giant ganglia within the submucous plexus [2, 21, 22, 24, 30]. The precise incidence and aetiology of this condition is unknown, but it is cited as a major cause of primary constipation, even commanding its own support group NIDKIDS in Australia [9].

The evidence collected upon this entity is, at first appearances, deceptively infallible. However, there is mounting concern that IND B is still a clinical diagnosis only and not a distinct histopathological entity. There is concern that the previous diagnostic criteria in fact describe the normal large-bowel ganglion cell population which, when recognised in a constipated patient, may even lead to surgical resection. The methodology used to describe the histopathological features of IND B can be readily criticised, and observations and developmental studies suggest that IND B may not exist as a distinct histopathological entity using the most widely recognised criteria.

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Methodological criticism

Comparing specimens which have been diagnosed histologically as IND B by virtue of the presence of giant ganglia with normal controls will, of course, prove only that in all the IND B patients giant ganglia are present and that in some of the normal controls they are not [17, 18]. The larger the study, the more significant this result will seem. If this selection bias is unrecognised, there is a danger of concluding that giant ganglia are a diagnostic feature of IND B.

It is also apparent that it is important to first define the normal appearances and quantify normal ranges of the elements to be examined in a study. Several figures for the percentage of ganglia within the submucous plexus of those suffering with the clinical features of IND B have been generated but insufficiencies in the normal control group are all too evident. Kobayashi et al. [13] obtained 10 controls from colostomy sites, but do not reveal what the colostomies were performed for. Similarly, Meier-Ruge et al. [22] obtained 92 normal controls but did not reveal the criteria for taking these biopsies and assessing them as normal. Small numbers of controls and patients also create difficulties in statistical analysis, with less accuracy of significance testing. Kobayashi [12] compared only 23 controls with 9 cases of isolated IND B, and thus difficult significance calculations with Fischer's exact probability test were needed. IND B is currently diagnosed by biopsy of the large bowel. Obtaining a set of controls presents a challenge, as it would be ethically unsound to put a "control" child through an unecessary surgical biopsy [16]. Koletzko et al. [14] cite this as a major problem with clinicopathological correlation studies in IND B. Meier-Ruge et al. [25] did obtain surgical biopsies from 20 normal control children, up to 15 cm from the pectinate line, and quotes a figure that up to 5% of ganglia are giant ganglia, but does not make it

clear if this is in normal controls or in patients with IND B. Perhaps the best answer is to use cadaveric material from traumatic death, in which there is no history of constipation and to take into account any possible post-mortem artefact.

Throughout the literature, terms such as "hyperganglinosis" and "hypoganglinosis" are applied freely and frequently and are often recognised as important features of IND B. However, although these words are applied frequently, their use is non-sensical when applied to the submucous plexus: as explained earlier, no-one has defined precisely how many ganglia and ganglion cells there are within the submucous plexus. Smith [37] addresses this problem in the myenteric plexus and accurately describes the counting of ganglion cells within normal and abnormal large bowel, suggesting that hypoganglionosis and hyperganglionosis occur when the number of ganglia are 2 standard deviations below or above the mean, respectively. A similar methodology could be applied to the submucous plexus.

Conveying to the reader the exact method used to perform a scientific study in order that the experiment will be reproducible is one of the cornerstones of all scientific literature. Indeed, in many of the papers examined concerning IND B, complex staining methods and explanations of the statistical tests used were well described and were therefore repeatable. However, the most basic elements within the methods were, on the whole, poorly described. Several sources quantitating ganglia and ganglion cells of the submucous plexus do not define how they identify a cell or whether they included cytoplasmic fragments in the counts or only used whole cells. The fundamental disease process examined, i.e. constipation, is also very poorly described on the whole [21–24, 28]. Loening-Baucke [17] defines constipation as a stool frequency of less than three a week in children. These poor definitions have led to considerable inter- and intra-observer variability. Meier-Ruge in three separate papers produced inconsistent percentages of giant ganglia, although the same methodology was applied throughout [22, 24, 25]. The large variety of methodologies used to describe the neuropathological features of the submucous plexus in constipated children has caused further confusion as to exactly what defines, if anything, IND B (see Lumb and Moore [18] and Schofield and Yunis [35] for details). Lake [16] in a previous editorial has described the confusion that has resulted from constantly changing diagnostic criteria as well as regional differences.

Thus, IND B has grown up around several studies with flawed statistical analysis and poorly defined methodologies with poorly defined and possibly inadequate controls and non-reproducibility of results, and yet it is printed in standard texts of pathology as an entity that a surgeon can treat by cutting out segments of bowel.

Developmental study

During development, the submucous nerve plexus develops from primitive neuroblasts derived from the neural crest. Under the influence of homeobox genes, the neuroblasts migrate through the mesenchyme surrounding the developing gut. They are primarily derived from a vagal source and, thus, migration predominantly occurs in a cranio-caudal direction. There is a smaller contribution from a sacral source. The myenteric plexus is sited first, which then gives rise to emigres moving dorsoventrally to form the submucous plexus [5, 11]. The precise mechanism of control of this migration is unknown; whether the migrating blast cells are attracted to their site of eventual maturation or are programmed to migrate to a point [1]. If either of these mechanisms were defective, one would expect that the number of ganglia would be reduced. To produce an area in which there were more ganglia than normal (and thus more giant ganglia), a physical barrier to the neuroblast cell migration would need to be present with continued migratory stimulus. Thus, the neuroblast cells would collect upon the edge of this obstruction and produce a segment with an increased number of giant ganglia, with the proximal portion most effected. Kotiloglu et al. [15] describe an obstructing mucosal web in the small intestine with numerous ganglion cells in the proximal segment. Sacher et al. [32] describe the features of IND B in association with ileal atresia, ileal stenosis and anterior located anus, but also note that it is associated with intussusception, volvulus and meconium peritonitis and propose that IND B is in fact a secondary phenomenon. However, it still remains that with present embryological knowledge, an isolated increase in giant ganglia (that is the feature of IND B) cannot be explained in terms of developmental abberation.

Observed findings against IND B

We observed that in resection specimens for rectal carcinoma, the tumour-free resection margins contained giant ganglia which constituted 10% of the total ganglia. Meier-Ruge et al. found that 3–5% [25] and 10% [24] of ganglia were giant in cases of IND B, which suggests that they were merely observing the normal number of giant ganglia. In one study, 56% of a group of adults with primary chronic constipation were diagnosed as having IND B on the basis of the presence of giant ganglia [38]. However, in our experience, ganglia containing more than seven ganglion cells can be found in over half of non constipated adult subjects.

A neurological deficit within the bowel, that causes constipation by rendering the bowel and stool immobile, should have physiological characteristics. However, manometric studies [14, 17, 34, 39] and a radiological study [39] did not find any such pathological physiology.

A disease process and its histological appearance should bear some relationship. Cord-Udy et al. [3] ex-

amined three groups of children, all of whom had presented in early childhood with intestinal dysmobility. Two of the three groups had diagnostic features of IND B on initial biopsy, and one group was histologically normal. There was no significant difference of continued symptomatology after 3–5 years, and absolute numbers of those with continued symptoms were higher in the latter (control) group. Csury and Pena [4] reviewed 25 publications and also concluded that there was no correlation between the histological criteria for IND B and the clinical outcome. Several publications disagree on how common IND B is [6, 19, 26] and this may indicate that this disease has not yet been properly identified or defined.

It is also reported that in those patients diagnosed as suffering with IND B there is an apparent recovery time [26, 39]. But how can this be so if, as originally suggested, IND B is a permanent dysplasia of the control mechanism for propelling a stool through the large intestine? Ryan [31] suggests that there may be some neuronal maturation, but also points out that IND B sufferers are also known to develop progressively worse symptoms. The precise function of the submucous plexus is not known. The most likely function of the most superficial group of ganglion cells (Schabadasch plexus) is secretomotor [33]. Failure of these cells may produce constipation refactory to lubricating laxatives.

Future research

In order to research entities that cause primary constipation, it is of paramount importance to first understand and characterise the normal features. Most laboratories use haematoxylin and eosin as the baseline stain [16], and any large study into the normal appearance of the enteric nervous system should be first characterised using this stain, detailing the precise staining method and section thickness. Meier-Ruge [21] notes many varying appearances of the innervation of the gut, and describes these as the non-classifiable dysganglinoses. However, which of these non-classifiable dysganglinoses is a normal variant?

Gittes et al. [6] discuss the possibility that IND B may in fact be a disease of unbalanced neuropeptides within the gut and cite vasoactive intestinal peptide and calcitonin-gene related peptide as possible culprits. Kobayashi et al. [13] describe a deficiency in growth-associated protein-43 in those diagnosed with IND B. Hutson et al. [10] describe a deficiency of substance P-reactive fibres in the submucous plexus. Hirobe et al. [7] suggest an immunological mechanism, with an excess of MHC II in the submucous plexus. Ryan [31] details an autoimmune paraneoplastic phenomena in a case of small cell carcinoma of the bronchus.

Recently Shirasawa et al. [36] produced homeobox-deficient mice, deleting the homeobox Enx (Hox11L1). This homeobox is thought to control the position of the enteric neurones in mice and, when deleted, can produce similar features to IND B, including a profound constipation, abdominal distension and retarded growth. Histology reveals that these mice, when compared to a normal control group, display an absolute increase in the number of ganglia in the myenteric plexus of the colon but not in the small intestine. Identification of a human homologue for this mouse gene may allow diagnosis of a subgroup of children with chronic constipation circumventing the difficulties of histological diagnosis.

Conclusions

Intestinal neuronal dysplasia provides a simple explanation of constipation, which easily satisfies the clinician and concerned parents. Up to 95% of constipation in children may in fact be functional [17], and the cure to this common problem does not lie within the jurisdiction of the paediatric gastroenterologist or surgeon. It is important to remember that not all diseases have an underlying histopathological appearance.

The publications reviewed on this subject are all disharmonic and contain inconsistencies and inaccuracies too numerous to enter into a single script. Perhaps, this is the best indication that we need to go back to the drawing board.

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