Autoimmune hepatitis (range 1–11 years), but in none of the LKM1 positive. Patients who do not fulfil the criteria for cessation of treatment or fail a trial of treatment withdrawal will require life-long immunosuppression with the lowest dose of steroid and azathioprine able to maintain normal liver function. Children presenting with an acute hepatitis illness or with acute liver failure are better treated in a specialised centre with facilities for paediatric liver transplantation. For those patients with established cirrhosis, liver decompensation, which may occur several years after diagnosis, should be treated by transplantation. The disease occasionally recurs after transplant.\(^\text{35}\)

Treatment with steroids and azathioprine is usually satisfactory in controlling the inflammatory process damaging the liver; progression to cirrhosis, despite treatment, however, is frequent. In addition, such treatment may have serious and unpleasant side effects. New immunosuppressive agents such as cyclosporin and tacrolimus have been anecdotally used in the treatment of autoimmune hepatitis. The role of these drugs, however, which have serious side effects such as nephrotoxicity and predisposition to the development of lymphoproliferative disorders and other malignancies, should be evaluated in trials conducted in specialised centres.

It is hoped that in the not too future a better knowledge of pathogenetic mechanisms of liver damage will lead to a more specific and effective therapeutic intervention.

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13 Wen L, Peckman M, Mowat AP, McElvany-Gergo, Vergani D. 6± T cell clones derived from liver biopsies of children with autoimmune chronic active hepatitis (aCAH) and primary sclerosing cholangitis (PSC) are cytotoxic to human liver target cells [abstract]. J Hepatol 1991; 13: S80.
17 Hirschprung's disease is a congenital condition (one in 5000 live births) characterised by aganglionic pyloric (Auerbach) and submucous (Meissner)plexes of the distal colon and a sustained contraction of this segment. In the majority of cases (80%), the aganglionic tract involves the rectum and the sigmoid colon only (short segment Hirschsprung's disease) while in 20% of cases it extends towards the proximal colon (long segment Hirschsprung's disease). Enlarged nerve trunks are present.

Hirschsprung's disease

Although it is over a century since Harald Hirschsprung first described congenital megacolon, only relatively recently has research endeavour begun to throw light on its pathogenesis and pathophysiology. It is the purpose of this annotation to review some of this recent evidence. Hirschsprung's disease is a common condition (one in 5000 live births) characterised by aganglionic pyloric (Auerbach) and submucous (Meissner)plexes of the distal colon and a sustained contraction of this segment. In the majority of cases (80%), the aganglionic tract involves the rectum and the sigmoid colon only (short segment Hirschsprung's disease) while in 20% of cases it extends towards the proximal colon (long segment Hirschsprung's disease).
in the submucosa and between the two muscle layers and contain abundant strongly acetylcholinesterase positive nerve fibres. The smooth muscle in the aganglionic segment has a normal tone and a normal excitation-contraction coupling mechanism and it responds to cholinergic and adrenergic agonists in a way that indicates normal functioning receptors. Thus the disease appears to be neurogenic in nature.

Genetic factors
Evidence that genetic factors contribute to Hirschsprung’s disease derives from the observation of an increased risk to siblings (2.4–9%) as compared with the population incidence, a dominant pattern of inheritance in several pedigrees of Hirschsprung’s disease and the frequent association with chromosomal abnormalities (for example, Down’s syndrome) and malformative syndromes (for example, Waardenburg’s syndrome). Although Hirschsprung’s disease is a heterogenous genetic disorder with autosomal dominant, autosomal recessive and polygenic forms, one autosomal dominant form has been mapped by linkage analysis to human chromosome 10q11.1.4,5 Moreover, mutations in the receptor tyrosine kinase RET proto-oncogene, which maps to 10q11.1, have been convincingly demonstrated.6 Receptor tyrosine kinase are cell surface molecules that transduce signals for cell growth and differentiation. RET proto-oncogene is a protein tyrosine kinase gene expressed in cells derived from the neural crest and may play a critical part in the embryogenesis of the mammalian enteric nervous system.7,8 Puffenberger et al have mapped a recessive susceptibility locus for Hirschsprung’s disease to a endothelin-B receptor gene on human chromosome 13q22.9 Endothelin-B receptor activation may also have an important role in the development and migration of human enteric ganglion cells.

Embryogenesis of the enteric nervous system
The enteric nervous system is formed by cells that migrate to the bowel from the neural crest. Hirschsprung’s disease is thought to be a neurocrystalopathy related to the premature arrest of the craniocaudal migration of neural crest cells toward the anal end of the rectum during the fifth to the 12th week of gestation. Whether the gradient of migration is single (proximodistal) or dual, with input from the sacral neural crest, has been a controversial issue.10-12 In human fetal models of Hirschsprung’s disease, however, neural crest cells have never been observed in the distal gut before their appearance in the proximal gut.13 Knowledge of the source of the neural crest cells is probably less important than understanding those factors which govern the migration, proliferation, differentiation, and colonisation of these cells in the fetal intestine. Identification of specific genes associated with Hirschsprung’s disease and characterisation of their gene products (such as receptor tyrosine kinase and endothelin-B receptor) is beginning to enhance our understanding of these processes.

Importance of the extracellular matrix in enteric neurogenesis
ANIMAL MODELS OF HIRSCHSPRUNG’S DISEASE
The terminal colon of the lethal spotted mutant mouse fails to become colonised by neural crest cells and thus remains aganglionic. Using this animal model of Hirschsprung’s disease, Jacobs-Cohen et al performed in vitro co-culture experiments to evaluate the ability of neural crest cells to migrate into bowel destined to become aganglionic versus bowel destined to become normal ganglionic bowel.14 Results showed that neural crest cells migrated into the bowel destined to become normal bowel but did not migrate into the bowel destined to become the aganglionic segment of the mutant mouse. The authors concluded that non-neuronal elements of the wall of the presumptive aganglionic region of the mutant mouse colon are abnormal and prevent the colonisation of this segment of gut with viable neural precursors from the neural crest. Other workers using the same model have also demonstrated that the primary defect in these mice embryos is not autonomous to enteric neuroblasts but exists in the non-neuroblastic mesenchyme of the large intestine.15

Further studies have attempted to identify the nature of the non-neuronal abnormalities in this segment of colon that could account for the migratory failure and have found high levels of the extracellular matrix glycoproteins, laminin and collagen type IV.16,17 These and other extracellular matrix proteins (for example, fibronectin, tenasin, and hyaluronic acid) play an important part in human enteric neurogenesis in early embryonic life and the evidence suggests that an (genetically determined?) ‘abnormal microenvironment’ in the wall of the colon prevents normal neural crest cell migration and may have a role in the pathogenesis of Hirschsprung’s disease.

Pathophysiology of colonic spasm
Whereas intrinsic ganglia are absent, extrinsic nerve axonal processes still enter the bowel wall and proliferate, where they stimulate unopposed contraction, resulting in functional obstruction of the aganglionic segment of the bowel. Thus the nerve fibres in the constricted (aganglionic) segment of the colon in Hirschsprung’s disease seem to employ contractile but not relaxing transmitters and the cause of the constriction would then be a predominance of neuronal elements that produce contraction and a relative shortage of those that produce relaxation.18 Inhibitory innervation of the gut includes intrinsic non-adrenergic, non-cholinergic (NANC) fibres and to a lesser extent extrinsic adrenergic fibres.

Nitric oxide – a novel chemical messenger
The key neurotransmitter in the NANC inhibitory control system is yet to be confirmed but recent evidence points to the excitatory messenger molecule nitric oxide (NO) as the likely candidate. NO is synthesised from L-arginine by nitric oxide synthase (NOS) and has been identified as an important mediator of relaxation of the gut musculature.19 Several recent studies have demonstrated that NO is absent in the aganglionic segment in Hirschsprung’s disease.20-22 Further evidence that lack of NANC nerves is the specific defect that induces bowel obstruction in patients with Hirschsprung’s disease was provided in an elegant study by Bealer and colleagues.23 A 70% reduction in resting tension was demonstrated after electrical field stimulation of isolated smooth muscle from aganglionic colon after exposure to an exogenous source (S-nitroso-N-acetylimidazol) of NO.23 This and other work, where topically applied NO (nitrate paste) has been used successfully in the treatment of achalasia,24 also points to potential future therapeutic advances in the management of Hirschsprung’s disease.

Peptidergic nerves
NANC innervation is thought to include several different populations of peptide-containing nerve fibres. Defects in the inhibitory peptide-containing nerves may account for the 20% of children who continue to have intestinal...
dysfunction after removal of the aganglionic segment. The remaining segment may appear normal as determined by routine histopathological methods which will not detect abnormalities of the peptide-containing nerves. 25 26

Studies of the peptidergic innervation of the aganglionic segment in Hirschprung's disease have revealed reduction or absence of a wide variety of neuropeptides including vasoactive intestinal peptide,27 28 pituitary adenylate cyclase activating polypeptide,29 enkephalin, gastrin related peptide, and substance P. 30 The functional role of these neuropeptides in the control of gut motility is unclear. Nevertheless, a synergistic effect on intestinal motility control between vasoactive intestinal peptide (VIP) and NO has been shown 19 and suggests that a lack of NO and VIP in nerve fibres in the aganglionic segment in Hirschprung's disease may contribute to or be responsible for the inability of the smooth muscle to relax, thereby preventing peristaltic waves.

Diagnosis

The diagnosis of Hirschprung's disease relies on pathological investigation of tissue sections using markers for neurons (neuron specific enolase, acetylcholinesterase, microtubule associated Tau protein) or neuron supporting cells (for example, glial fibrillary acid protein, glutamine synthetase, soluble protein). The greatest assurance of reaching an accurate and definitive biopsy diagnosis of Hirschprung's disease is considered to be provided by examination of both haematoxylin and eosin and acetylcholinesterase stained sections of full thickness rectal mucosa.

Conclusion

Current evidence on the pathogenesis of Hirschprung's disease, then, favours the 'abnormal microenvironment' hypothesis wherein the developing and migrating normal neural crest cells confront a segmentally abnormal and hostile microenvironment in the colon. This hypothesis would account both for the congenital absence of ganglion cells in the wall of colon and also for the range of enteric neuronal abnormalities encountered including neuronal dysplasia, hypoganglionosis, and zonal aganglionosis. The abnormal constitution of the mesenchymal and basement membrane extracellular matrix in the affected segment of colon is presumably genetically determined and further understanding of the pathogenesis of this disorder will emerge as molecular geneticists characterise the specific genes and gene products associated with Hirschprung's disease. Advances in this field should permit gene probes to be developed to facilitate prenatal and postnatal diagnosis.

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