Annotations

Neonatal origins of schizophrenia

Schizophrenia is not an illness which impinges much upon the daily practice of paediatricians or, indeed, child psychiatrists, as only a tiny proportion of diagnosed cases (< 5%) arise before the age of 16 years. Schizophrenia is one of the few chronic diseases which arise principally during late adolescence and early adulthood, normally the healthiest period of life. There is increasing evidence, however, that neurodevelopmental factors, acting in utero and in early childhood, are important in determining the risk for later schizophrenia.1

Genetic risk

There is no doubt that genetic factors are involved in the aetiology of schizophrenia.2 First degree relatives of patients have a morbid risk of developing schizophrenia which is eight to 10 times higher than the risk in the general population; this risk rises to approximately 50% in the identical twins of schizophrenics. Now that a neurodevelopmental aetiological model is considered most likely, genes that control early development have come under particular suspicion. Unfortunately, in spite of an intensive effort to locate and identify susceptibility genes for schizophrenia, none has yet been found.3

Environmental risk

The fact that the monozygotic concordance rate for schizophrenia is only 50% indicates that environmental factors must also be involved, and simple additive models suggest that between 20–30% of the variance in liability to schizophrenia may be attributable to non-genetic factors. What are these environmental factors and how might they operate?

PERINATAL COMPLICATIONS

Schizophrenic patients, as a group, experience a greater number of birth complications than controls.4 Inspection of the particular complications associated with schizophrenia suggests that hypoxic-ischaemic brain damage may be the common mechanism.5 Schizophrenics who have suffered perinatal complications are especially likely to show lateral ventricular damage and decreased volume of the hippocampus. Recent findings from a 28 year follow up of a Finnish birth cohort have shown that children with perinatal brain damage (defined as neonatal convulsions, low Apgar scores, asphyxia, intraventricular haemorrhage, or abnormal neurological signs in the newborn period) were seven times more likely to develop schizophrenia in adulthood than the remainder of the cohort.6 These results indicate that almost 7% of schizophrenia in the general population might be attributable to this factor. Labour and delivery complications are relatively common in the general population, however, and only rarely are associated with schizophrenia. Therefore, for schizophrenia to result, either a particular neuronal system must be damaged or the individual must carry genetic vulnerability.

FETAL MALDEVELOPMENT

A number of studies have shown that schizophrenics are more likely to have had low birth weight and decreased head circumference at birth.7 Minor physical abnormalities and dermatoglyphic abnormalities, which are thought to represent “fossilised” evidence of early developmental deviance, also occur to excess in schizophrenia,8 as do cortical cytoarchitectural changes which are consistent with disturbances of development during gestation.9 These indicators of fetal maldevelopment may indicate environmental insult to the fetus. A study of monozygotic twins discordant for schizophrenia has shown that the affected cotwin had more markers of prenatal developmental disruption than the unaffected twin,10 and a comparison of familial and non-familial schizophrenics showed that minor physical anomalies were more likely to occur in the latter.11 Complications of pregnancy which have been associated with schizophrenia include prenatal exposure to influenza,12 prenatal nutritional deprivation,13 and rhesus incompatibility.14 The mechanism of action of these effects is not yet elucidated and effect sizes are small. The association with influenza may reflect a neurotoxic effect of influenza on the fetal brain, or an effect related to maternal immunological responses to infection. The association with rhesus incompatibility may be mediated through fetal hypoxia resulting from haemolysis.

CHILDHOOD CENTRAL NERVOUS SYSTEM INFECTIONS AND EPILEPSY

Data from the same Finnish cohort as discussed above, showed that individuals who had suffered a viral central nervous system infection during childhood were almost five times more likely to develop schizophrenia than the comparison group.15 The incidence of schizophrenia was particularly high, at 12.5%, among a group of 16 individuals who had contracted neonatal cosackie B meningitis during an epidemic in one maternity unit. The incidence among the rest of the study population was 0.7%. Patients with schizophrenia in this series were also two to three times more likely to have a history of childhood epilepsy than the rest of the study population.
CHILDHOOD DEVELOPMENTAL ABNORMALITIES

High risk studies
Developmental abnormalities during different stages of childhood have been found in 25–50% of children born to schizophrenic mothers ("high risk" children).20 21

These include: (1) hypoactivity, hypotonia, and poor "cuddliness" during the neonatal period; (2) a disordered pattern of acquisition of milestones in infancy; (3) "soft" neurological signs, in particular poor motor coordination in early childhood; and (4) deficits in attention and information processing in late childhood.

These findings indicate that at least part of the genetic vulnerability to schizophrenia is manifest through abnormal neurodevelopment. Follow up will continue on these high risk samples to determine whether the children who have displayed such neurodevelopmental abnormalities will go on to develop schizophrenia.

General population birth cohort studies
Similar findings have been reported among the 1946 British birth cohort. This cohort of 4746 British children, who were born in one week in March 1946, has been studied on over 20 occasions up to the age of 43 years. The 30 children who went on to develop schizophrenia as adults could be distinguished from their peers in these ways:22

- Motor developmental milestones, in particular walking, were delayed by an average of 1.2 months
- More speech problems (odds ratio (OR) 2.8)
- Lower educational test scores at ages 8, 11, and 15
- Preference for solitary play at ages 4 and 6 years (OR 2.1).

Home movies' studies
A unique collection of "home movies" depicting schizophrenic patients during childhood shows that the preschoolerhcann children can be distinguished from their siblings, with a high degree of accuracy, by the presence of subtle abnormalities of motor tone and facial expression.23 Retrospective studies have shown that preschool schizophrenic children have markedly poorer overall social adjustment in childhood than normal controls or children destined to develop affective psychosis.24

Gene-environment interaction
Although having an affected relative remains the strongest risk factor for schizophrenia (table 1), there are many prenatal and postnatal risk factors with smaller effect sizes which cannot be ignored. These environmental risk factors may act additively with each other or may indicate the existence of gene environment interactions.25 Birth complications or adverse psychosocial circumstances in childhood may interact with genetic vulnerability to increase the risk of psychosis.26 For example, there is a greater risk of schizophrenia among genetically vulnerable children who were placed in poorly functioning adoptive homes compared with those placed in well functioning homes,27 and high risk children reared in a kibbutz had increased rates of schizophrenia compared with those who were reared in family homes.28 In other words, the pathogenic effects of adverse social circumstances appears to increase risk of schizophrenia only in children who have some degree of genetic vulnerability.

Conclusion
An important clinical implication of the prenatal and neonatal risk factors mentioned in this paper is that some forms of schizophrenia may be preventable. Environmental agents can be more easily manipulated than genetic factors. Avoidance of perinatal hypoxia, nutritional supplementation during pregnancy, and prevention of central nervous system infection in childhood, particularly neonatal coxsackie B infection, may help reduce the incidence of schizophrenia. We are still a long way, however, from testing the efficacy of such measures, or indeed from developing an accurate screening test for schizophrenia. Although children destined to develop schizophrenia in adulthood have been shown to differ from their peers in social and intellectual function, these behavioural and cognitive risk factors are non-specific and cannot be applied to the general population. Close observation of children who are genetically vulnerable to schizophrenia, may prove useful in this regard. Measures such as careful supervision of adoptive or foster home placements, social skills training, protection from stressors, and early referral to psychiatric services could help prevent psychotic breakdown among high risk children. Although definitive evidence for such measures is lacking, early treatment of psychosis has been shown to improve prognosis,29 and studies of prevention in schizophrenia are already underway. In conclusion therefore, study of the neonatal and childhood precursors of schizophrenia allow the possibility of prevention and early intervention in at least some cases of the disorder. Although this research is in its early stages, it may not be necessary to wait until the gene or genes for schizophrenia are discovered to begin reorienting our approach to this devastating illness.

Table 1  "Best estimate" effect sizes of various genetic and environmental risk factors for schizophrenia (expressed as odds ratios or relative risks)

<table>
<thead>
<tr>
<th>Category of risk factor</th>
<th>Specific risk factors</th>
<th>Best estimate of effect size</th>
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<tbody>
<tr>
<td>Genetic*</td>
<td>Monozygotic twin of schizophrenic patients 46</td>
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</tr>
<tr>
<td></td>
<td>Dizygotic twin of schizophrenic patient 14</td>
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<tr>
<td></td>
<td>Child/sibling of schizophrenic patient 10</td>
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<tr>
<td>Childhood developmental†</td>
<td>Delayed milestones 3</td>
<td></td>
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<td></td>
<td>Speech problems 3</td>
<td></td>
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<tr>
<td>Prenatal and postnatal environment†</td>
<td>Perinatal brain damage 7</td>
<td></td>
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<tr>
<td></td>
<td>Rheus incompatibility 3</td>
<td></td>
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<tr>
<td></td>
<td>&quot;Unwanted&quot; pregnancy 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe undernutrition (1st trimester) 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maternal influenza (2nd trimester) 2</td>
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*Relative risks; †odds ratios.

Key messages
- Most schizophrenics have subtle brain abnormalities of developmental origin, and many show impairments of motor, cognitive, and social function in childhood, decades before the onset of frank psychosis. These findings have led to the conclusion that schizophrenia is a neurodevelopmental disorder
- The strongest risk factor for schizophrenia is having an affected relative. Prenatal and perinatal risk factors, in particular prenatal viral exposure and fetal hyopxia, also appear to be important
- An important clinical implication of the existence of prenatal and neonatal risk factors is that some forms of schizophrenia may be preventable

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Benign childhood occipital seizures

Benign childhood epilepsy with centrotemporal spikes or rolandic epilepsy is well recognised,1–3 but benign childhood occipital seizures (BCOS) are not widely known.1–7

BCOS have a prevalence of 20–25% among benign childhood partial seizures, with two clinical forms: early onset BCOS described by Panayiotopoulos4–6 and late onset BCOS of Gastaut.4 Idiopathic photosensitive occipital seizures are also well documented.4–10

Early onset benign childhood occipital seizures

Seizures consist of autonomic and behavioural disturbances with vomiting and deviation of the eyes lasting from minutes to hours. They are mainly nocturnal and often progress to convulsions. Consciousness is usually impaired from onset or during the ictus. By definition, seizures lasting for more than half an hour are status epilepticus. In one third of these children, the phase of deviation of the eyes with vomiting and impairment of consciousness is prolonged for more than 30 minutes (partial status epilepticus), and usually ends with generalised convulsions. A typical case is of a child who wakes up from sleep agitated, vomiting, eyes deviated to one side, and who may or may not be able to communicate for minutes to hours before hemiconvulsions or generalised convulsions begin. Onset is between 1–12 years, peak is at 5 years, and remission occurs within 1–2 years from onset. In one third of the patients, seizures or even partial status epilepticus are single events in the child’s life. The mean total of seizures is three and the maximum is 15.1 Early onset BCOS are entirely benign. Only four out of 113 children with early onset BCOS developed rolandic seizures, and only one continued with infrequent generalised convulsions.1 A grave neurological condition may be suspected during the prolonged ictus but the normal state after ictal should be reassuring.

The electroencephalogram manifestations are severe with long runs of high amplitude occipital sharp and slow waves. They often appear when the eyes are closed because they are activated by the elimination of fixation and central vision (fixation-off sensitivity).4,5 Spikes in the centrotemporal or other locations occur in 10–30% of patients.1

There is no photosensitivity. Occipital spikes should raise the possibility of BCOS, but they may also occur in children who do not suffer from seizures and in those with severe symptomatic epilepsies.4 Furthermore, 10% of children with early onset BCOS may have a normal interictal electroencephalogram.1–7

Late onset benign childhood occipital seizures

Seizures manifest with visual hallucinations and/or blindness, they are frequent, mainly diurnal lasting from seconds to less than three minutes. They may progress to other seizure manifestations, mainly hemiconvulsions. Loss of consciousness may occur with or without convulsions. A postictal headache occurs in 30% of patients. Mean age at onset is 7–8 years, and prognosis is usually good with remission often occurring within two to three years.

The electroencephalogram is identical to that of the early onset BCOS with occipital paroxysms when the eyes are closed.1–7

The differential diagnosis of late onset BCOS from basilar migraine or migraine with aura has been recently detailed.11 The main cause of misdiagnosis is that visual hallucinations are often not evaluated quantitatively and qualitatively.11 Instead, they are erroneously abbreviated in terms such as fortification spectra, teichopsis, scintillating scotomata, phosphenes, and their variations, whose meaning often misrepresents the actual descriptions of the patients.

In epileptic seizures, elementary visual hallucinations are frequent, nearly daily, and short — they usually last from a

References

1 Asarnow RF, Asarnow JR. Childhood onset schizophrenia. Schizophr Bull 1991;17:589–606.

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few seconds to less than three minutes. They consist of predominantly multicoloured circular patterns, “hundreds of brilliant small balls of many colours”. Onset is always on the same side. These visual fits may progress to other motor partial seizures, loss of consciousness, and convulsions. Postictal headache is rarely throbbing and severe. Intercital electroencephalogram occipital spikes usually reveals their epileptic nature.

In migraine with aura, visual hallucinations are prolonged, developing over more than three minutes and lasting for 20–30 minutes. They are not as frequent as those in BCOS. They are characterised by predominantly black and white linear and zigzag patterns. Colours may be described, but they are usually not predominant and occur in the periphery of the visual hallucinations along with the zigzag bright streaks or flashes of light. Side alteration between attacks is frequent. Photophobia and irritation are common. Throbbing headache and vomiting follow.

In basilar migraine, bilateral visual hallucinations similar to those of migraine with aura or blindness are associated with brain stem symptoms of vertigo, ataxia, tinnitus, and peripheral dysaesthesias. These are followed by severe, throbbing, posterior, bilateral headache occurs. Impairment of consciousness may occur in a quarter of the cases, usually between the aura and the headache. It is usually brief, from one to 10 minutes, with features distinguished from epileptic seizures. It is slow in onset, never abrupt, and never causes the patient to fall or to be injured. Prolonged and severe impairment of consciousness are rare. In between these attacks classical migrainous episodes with aura may occur. The interictal electroencephalogram is usually normal, but slow wave abnormalities are seen during the attacks.

**Epilepsy or seizures?**

The term epilepsy, even in its strict definition of at least two unprovoked seizures, is not appropriate for 30% of the children with early onset BCOS who have only one fit. They consider that the other 70% of these children should not be discriminated and labelled with “epilepsy” just because they have two or more seizures. Preferable terms are benign childhood partial seizures or benign childhood seizure susceptibility syndromes, denoting an idiopathic liability to seizures and/or electroencephalographic manifestations which are age specific. The risk of recurrent seizures in adult life is less (1–2%) than in febrile convulsions (4%).

**Treatment**

The conclusion from a recent study on early onset BCOS is that “treatment may not be warranted”. This is certainly the case for the 30% who have only one seizure in their life. The remaining 70%, with an average of three seizures, also may not need medication. If treatment is considered necessary, carbamazepine, sodium valproate, and phenobarbital are equally effective. Carbamazepine is preferred because of fewer side effects. It is important to remember that remission occurs within one to two years after the first seizure, and antiepileptic medication should be withdrawn after this period.

When early onset, BCOS presents with partial status epilepticus which may be prolonged for hours and terminate with generalised convulsions. This needs urgent treatment with intravenous diazepam. Rectal diazepam should be prescribed for recurrent partial status epilepticus as for febrile convulsions.

In late onset BCOS, seizures may be very frequent, often daily. They usually respond well to carbamazepine which may be needed for two to four years.

**Unified concept of benign childhood partial seizures**

Benign childhood partial epilepsies, classified among the “age and localisation related idiopathic epilepsies” may be unified as they share common clinical and electroencephalographic characteristics and one may evolve into another. Seizures are infrequent or solitary, usually nocturnal, and decrease within one to three years from onset. Ictal hypersalivation, vomiting, headache, pallor, or sweating, unusual in other epileptic syndromes, are frequent and may occasionally appear in isolation. Despite normal development, normal brain imaging, and rarity of seizures, the abnormalities on the electroencephalogram are severe and exaggerated by drowsiness and sleep. Similar features on the electroencephalogram, resolving with age, are found in 1–2% of asymptomatic children of school age.

**Idiopathic photosensitive occipital seizures**

Reflex epilepsies are classified as “epilepsies characterised by seizures with specific modes of precipitation” but if seizures persist, long-term medication with sodium valproate may be necessary.
Gastrointestinal problems in the immunosuppressed patient

The gastrointestinal tract is a major component of the human immune system with a total lymphoid mass which is comparable with bone marrow. The Peyer’s patches are the principal sites of interaction among luminal antigens and lymphocytes, while the scattered lymphocytes in the lamina propria and epithelium are the effector cells that mediate immune response. The gut is also a site of synthesis and release of a specialised form of immunoglobulin A (secretory IgA) which is resistant to digestion. These immunological mechanisms are important because the gut has a huge surface area which interacts with the numerous potentially noxious agents including micro-organisms and dietary antigens. The intestinal tract is also one of the most metabolically active tissues in the body, with mucosal renewal taking place every three to five days, it is not surprising therefore that the gut is often the target organ for pathological processes in the immunosuppressed patients. The deleterious effects of immunosuppression on the integral functioning of the gut are assuming greater importance now that the use of potent long term immunosuppression has become widespread, for example in autoimmune diseases and organ transplantation.

Pathophysiology of immunosuppression on gastrointestinal function

The effects of immunosuppression on the gastrointestinal tract are multiple and include loss of gastric acidity, impaired immune response, reduced mucosal integrity, and compromised mucosal regeneration.

The suppression of gastric acid secretion

This may be induced by treatment with H2 blockers or be secondary to malnutrition or immaturity (as in neonates), and the number of viable organisms surviving passage through the stomach can therefore increase by a 1000-fold causing gastroenteritis.

The immune response

The immune response may be globally attenuated by drugs such as steroids (reduction in chemotaxis and kinin production), or more specifically by cyclosporin A and tacrolimus, which inhibit T lymphocyte proliferation by inhibiting expression of interleukin 2. Such immunosuppression may cause persistence of normally mild infections such as cytomegalovirus or cryptosporidium, and permit an increase in commensal organisms. Epstein-Barr virus which infects B lymphocytes can induce B cell proliferation and ultimately B cell lymphoma in the presence of altered immune response. In transplantation, intestinal graft-versus-host disease (GVHD) is a risk when the mass of donor lymphocytes received is comparable with that of the recipient’s, as is the case in allogenic bone marrow transplantation or even small bowel transplantation. This risk is increased when the immune system is further suppressed with potent treatments such as OKT3 and antithymocyte globulin.

Mucosal injury

Mucosal injury is well documented in patients with chronic immunosuppressive states. Loss of intestinal integrity is a recognised sign of rejection in small bowel transplantation. Mucosal damage (mucositis) frequently occurs after tumour chemotherapy and after conditioning treatment before allogenic bone marrow transplantation in adults, but probably occurs less commonly in children. Radiation has been shown to cause inflammatory changes in the lamina propria in human adults. A protein losing enteropathy was reported to occur in up to 90% of paediatric bone marrow transplants, and this is associated with hypoalbuminaemia which may contribute to impaired regeneration of the villi.

Aetiologies of intestinal dysfunction

Infections

The gastrointestinal tract is a portal of entry for numerous pathogens, and infections are a major cause of morbidity and mortality in immunosuppressed patients. Common viral agents include rotavirus, cytomegalovirus, adenovirus, and coxsackie A virus, all of which may cause devastating diarrhoea in these patients. Bacterial infections include Campylobacter jejuni and salmonella, which are normally sensitive to gastric acid, and so are a particular risk in patients receiving H2 blockers. Clostridium difficile infection, which is associated with the use of broad spectrum antibiotics as is common in immunosuppressed patients, may sometimes lead to pseudomembranous colitis. Fungal infections are extremely common ranging from superficial candidiasis to severe systemic infections with candida or aspergillosis involving the intestine and closely related organs such as the liver and spleen. Infection by protozoa may also be a problem, and Pneumocystis carinii and cryptosporidium are the most frequently identified commensal organisms. Strongyloides stercoralis is a nematode which may cause a fulminating infection in immunosuppressed patients from the tropical countries.

Drug toxicity

Immunosuppressive drugs can cause a variety of gastrointestinal lesions including mucosal erosions, bleeding, and viscus perforation (for example, steroids); hepatitis, cholestasis, and pancreatitis (for example, azathioprine); impaired enterocyte function causing malabsorption (for example, mycophenolate and tacrolimus). Cytotoxic drugs (for example, cyclophosphamide and busulphan), and irradiation used as primary or adjunctive treatments with immunosuppressive agents cause an enteritis associated with gut mucosal ulceration and bleeding. Idarubicin has been associated with more diarrhoea than cyclophosphamide after allogenic bone marrow transplantation, necessitating support with parenteral nutrition. The use of isolated parenteral nutrition itself, however, may worsen gastrointestinal function because enteral feeding is an important stimulus to pancreatic function, villus growth, and mucosal integrity.

Immunological reactions

GVHD may cause inflammation in the gut stroma and degeneration and necrosis of crypt cells in which apoptotic bodies are characteristically seen. A severe form of diarrhoea, often containing blood and albumin, may ensue. Acute GVHD is a systemic disorder typically involving skin and liver in addition to the gastrointestinal tract; other organs such as the lungs and pancreas may also be involved. It usually occurs seven to 50 days after bone marrow transplantation (and occasionally after liver or small bowel transplantation). The damage GVHD causes to the liver is focused in the portal tracts with loss of bile
ducts and cholestasis, while the parenchyma is relatively spared. Lymphoproliferative disease that develops after transplantation may be considered as an “opportunistic cancer” in which the immunodeficiency state of the host has a key role in fostering the environment necessary for abnormal lymphoproliferation. The development of lymphoproliferative disease after transplantation (usually leading to undifferentiated B cell lymphoma) may be related to exposure to Epstein-Barr virus, chronic antigenic stimulation from the allograft, or a direct oncogenic effect of immunosuppression. After a heart transplant, approximately 10% of patients develop lymphoproliferative disease, and 10–15% of small bowel transplant recipients may develop this disease also. The gut is a common site for the lymphoma to occur and may cause symptoms of obstruction, perforation, bleeding, and diarrhoea as well as chronic anaemia.

**VENO-OCCCLUSIVE DISEASE**
The peripheral branches of the hepatic veins are susceptible to occlusion by microthrombi, especially after bone marrow transplantation. The mortality rate is up to 30%, with a higher risk for patients who have a history of pretransplant viral hepatitis, radiotherapy, and busulphan conditioning. The increased hepatic venous pressure produces a Budd-Chiari like syndrome with unexpected weight gain and ascites.

**Patterns of gastrointestinal disorders**

**FEED INTOLERANCE**
Feed intolerance is common in immunosuppressed patients and is usually manifested by vomiting and diarrhoea, which may contain frank blood. These symptoms may be related to infections such as bacterial overgrowth and to mucosal inflammation, GVHD, or enteroocyte dysfunction. The presentation of infectious diarrhoea may be atypical in that an agent which usually produces superficial lesions in the mucosa may mimic another disorder such as Crohn’s disease. Mucositis induced by chemotherapy and total body irradiation is common in allogenic bone marrow transplantation, and up to half the transplant recipients in one paediatric study required two to four weeks of parenteral nutrition. Intestinal GVHD occurs in 30–70% allogenic bone marrow transplant recipients and may provoke a severe diarrhoea.

**SECRETORY DIARRHOEA**
This takes the form of a watery stool containing >60 mmol/l of sodium and may occur in isolation as a result of GVHD, cytomegalovirus, or rotavirus. In patients with chronic immune suppression, secondary to human immunodeficiency virus octreotide has been tried to control the secretory diarrhoea. A secretory state may also develop after small bowel transplantation.

**ABDOMINAL PAIN**
Abdominal pain may occur in severe GVHD, but other causes such as gastritis, typhlitis, or paralytic ileus are more common. Veno-occlusive disease causes a tender hepatomegaly.

**JAUNDICE**
Jaundice may be secondary to GVHD, veno-occlusive disease, sepsis (especially fungal), viral hepatitis such as cytomegalovirus, lymphoproliferative disease, or biliary sludge, which is common in patients who are receiving parenteral nutrition because of feed intolerance.

**MALABSORPTION**
Malabsorption is manifested by copious watery diarrhoea in which stools test positive for reducing substances and may contain fat if cholestasis or pancreatic dysfunction is present. Villus atrophy and mucositis result in a reduction in absorptive surface and marked carbohydrate malabsorption.

**BLEEDING**
Bleeding presenting as haematemesis, melaena, and rectal bleeding is common after major surgery and bone marrow transplantation. It may be related to the direct mucosal damaging effects of the drugs (steroids), poor anastomotic healing, anastomotic ulceration, or to haemorrhagic colitis/enteritis related to the infectious agents (for example, cytomegalovirus). Impaired platelet function and prolonged clotting times may also contribute to intestinal bleeding.

**PERFORATION AND OBSTRUCTION**
Perforation or obstruction, or both, are uncommon but may occur after cytomegalovirus enteritis, or steroid induced peptic ulceration. Silent perforation may sometimes occur in some of the patients (especially those with previous abdominal surgeries or underlying pathologies such as duodenal ulcers) who are receiving high dose corticosteroids, especially in the immediate period after the transplant. Transmural lymphoproliferative disease may perforate or obstruct the intestinal lumen.

**Diagnosis**
The patterns of symptoms and signs vary in severity, and overlap despite different aetiologies, so investigation is crucial in order to make a specific diagnosis. The most useful tests screen for infection, malabsorption, and histological evidence of tissue damage mediated either by the immune system, chemotherapy, or infectious agents.

**First line screening investigations**

**STOOL CULTURE AND ELECTRON MICROSCOPY**
These processes can identify up to three quarters of the infectious agents. Semiquantitative polymerase chain reaction (PCR) on circulating white cells reliably identifies cytomegalovirus infection and is soon likely to be applied to other tissues for other antigens (Epstein-Barr virus, for example).

**FACIAL STEATOCRIT**
Facial steatoctrit (greater than 2% fat in a 2 ml stool sample), faecal chymotrypsin (a marker of pancreatic enzyme function), and faecal reducing substances all suggest malabsorption. Protein malabsorption suggests a submucosal injury is present (for example, GVHD) and was shown to be present in 47% of children after bone marrow transplantation in a study by Papadopoulou et al. A protein losing enteropathy also occurs when the portal pressure is raised as in veno-occlusive disease. A faecal α1-anitrypsin of more than 2.2 mg/l of stool is indicative of a protein losing enteropathy.

**ENDOSCOPY**
Endoscopy provides direct visualisation for biopsy of mucosal lesions and can localise the site of blood loss. Light microscopic examination of the tissue biopsy specimens can provide conclusive evidence for GVHD, lymphoproliferative disease, cytomegalovirus, villous atrophy, inflammation, and rejection (in the case of small bowel transplant).
RADIOLOGY
Radiology, including plain abdominal x ray and abdominal ultrasound, can detect obstruction and perforation, anastomotic leak, toxic megacolon, features of acute pancreatitis, mucosal oedema, ascites or fluid collections, and visceral candidiasis. 27

Second line investigations
ABNORMAL LIVER FUNCTION
When abnormal liver function test results develop, it is extremely useful to take a biopsy specimen from the liver for identifying microabscesses, GVHD, veno-occlusive disease, and drug toxicity. The risks of bleeding, however, are high in allogeneic bone marrow transplantation because of marrow aplasia resulting in thrombocytopenia, and the recipients may have coagulopathy from other problems such as sepsis and GVHD. Therefore, blood product support and ultrasound guidance of the biopsy needle is recommended. Transjugular liver biopsy may be a safer option in older children after allogeneic bone marrow transplantation, where necessary.

RADIONUCLIDE IMAGING
Radionuclide imaging using white cell labelling may be helpful in delineating the site of gut inflammation/abscesses, but steroid administration (leading to impaired neutrophil function) and reduced white cell counts are common in immunosuppressed patients and limit the usefulness of this test. 26 In brisk gastrointestinal bleeding, technetium-99m labelled red blood cells can scan localise the site with diagnostic yield comparable with angiography.

INTESTINAL PERMEABILITY
Intestinal permeability is increased whenever the tight junctions between enterocytes are impaired by oedema, as in surgery to the intestinal tract, during gastrointestinal infections, after bone marrow transplant, and during acute cellular rejection after small bowel transplantation. 29 Intestinal permeability can be simply measured by analysing the differential absorption of two non-metabolised carbohydrates, but it is more useful in research than clinical practice.

Management
The non-specificity of gastrointestinal symptoms and the great diversity of potential pathologies affecting immunosuppressed patients mean that it is essential to make a precise diagnosis. Opportunistic infections or bacterial overgrowth may require specific treatment (for example, ganciclovir for cytomegalovirus, enteral immunoglobulin for adenovirus infection, 28 metronidazole for bacterial overgrowth, and co-trimoxazole for pneumocystis) and reduction in immune suppression if possible. Granulocyte colony stimulating factor may be helpful in patients with severe neutropenia. In small bowel transplant recipients, infection, or altered permeability is a manifestation of graft rejection and, paradoxically, the dose of the immunosuppressants may need to be increased at the same time as instituting broad spectrum antibiotics. Acute GVHD is managed using a combination of high dose corticosteroids and cyclosporin, with antithymocyte or antilymphocyte globulin used as a second line treatment. Azathioprine and thalidomide are useful in the treatment of chronic GVHD. Ursodeoxycholic acid may be valuable if the GVHD is damaging the bile ductules. 31 The use of irradiated blood is presently considered the most effective method of preventing GVHD after transfusion. 32 The management of veno-occlusive disease is supportive using diuretics and fluid restriction with thrombolytic agents such as alteplase (tissue type plasminogen activator) for severe and progressive cases. 33 Gastrointestinal bleeding may occasionally require surgery if medical treatment with H, blockers, proton pump inhibitors, and sucralfate fails. Nasogastric tube feeding with high energy feed is an important method of improving the nutritional status and gastrointestinal function of immunosuppressed children. 4

Summary
Gastrointestinal dysfunction is common in immunosuppressed children. It is almost invariably multifactorial, and often presents a diagnostic dilemma. Systematic investigation should allow an accurate diagnosis to be made so that immunosuppressed children can benefit from effective and timely interventions and may return to normal health more quickly and completely.

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