Silent gastro-oesophageal reflux: how much do we miss?

Gastro-oesophageal reflux in infancy is usually self evident and easily controlled. In most children, symptoms resolve by 18 months and only a minority develop oesophagitis, an iron deficiency anaemia, peptic oesophageal strictures, failure to thrive, or obstructive airways disease. Resolution is by no means lifelong, and many readers will not be surprised to learn that symptomatic reflux (heartburn) occurs daily in 7% of hospital medical staff, and at least monthly in 36%. During the 1980s, interest in this disorder was given fresh impetus. First, by the availability of oesophageal pH monitoring, a more accurate method of diagnosis than a barium meal. It is disappointing that despite its accuracy and ease of use, it is still used by less than a quarter of paediatricians in the UK. Secondly, a novel prokinetic agent, cisapride, became available and this was effective in controlling the symptoms of reflux and some of its complications. It also became clear that in some children reflux was clinically silent and that this was potentially more of a problem than the child with frequent regurgitation. Two circumstances in particular spring to mind: (i) the infant with recurrent apnoeas, so called apparent life threatening events (ALTEs), in whom reflux is now recognised to be common and potentially fatal and (ii) the child with cerebral palsy, in whom there may be resistance to appropriate investigation and treatment.

Gastro-oesophageal reflux and ALTEs

Considerable uncertainty remains even about which system to investigate first when an infant presents with a history of ALTE and when clinical pointers are absent. The cause may be subtle and difficult to diagnose. Up to three quarters of affected infants have pathological gastro-oesophageal reflux, and it is therefore appropriate to address its importance in the pathogenesis of ALTEs. Reflux is more likely if the ALTE occurred while the infant was awake, within two hours of a feed, or required vigorous stimulation by mouth to mouth resuscitation. It is crucial to note that in infants with ALTE the presence of vomiting or frequent regurgitation is a poor guide to pathological reflux.

For some time now the association between gastro-oesophageal reflux and ALTEs has been thought to be causal, partly because of the similarities in age and sex distribution between the two groups of affected infants. Until recently, firm proof of this association has been lacking. In part, this has been because of the lack of a close temporal relationship between reflux and apnoea. In a study of 24 infants with apnoea, or a history in a sibling of sudden infant death, it was not possible to show that a sudden fall in oesophageal pH, not necessarily below 4, induced central or obstructive apnoea, or vice versa. None the less, reflux was present in all 12 subjects who showed obstructive pauses during sleep. In a study in which arterial oxygen saturation was monitored using pulse oximetry, episodes of arterial oxygen desaturation (to less than 90% for over 3 minutes) occurred within 4 minutes of a fall in oesophageal pH below 4 in the 14 subjects shown to have gastro-oesophageal reflux out a total group 16 infants with ALTE. Pneumocardiograms were normal throughout. Infants with ALTE had a high incidence of reflux during sleep. The effect of oesophageal acidification on oxygen saturation was further assessed by administering apple juice (pH 3.5). While this had no effect on arterial saturation in controls, 50% of infants with ALTE demonstrated substantial acid induced decreases. Episodes of reflux occur more frequently in infants when awake than when asleep, although when episodes do occur during sleep they tend to be of longer duration. This is true both in infrequent episodes of physiological reflux and in infants with pathological reflux. It now seems that the duration and not the frequency of these episodes during sleep may be an important determinant of both reflux associated respiratory disease and sudden infant death. Identification of those infants in whom gastro-oesophageal reflux is a significant contributory factor in their obstructive airways disease has long been a problem. In an early study it was suggested that the mean duration of reflux episodes during sleep provided the best separation between patients with and without reflux induced respiratory symptoms. Ninety four per cent of children whose respiratory symptoms ceased with control of reflux had a mean duration of sleep reflux of over 4 minutes, while all those with respiratory symptoms unrelated to reflux had a mean duration of less than this. In a much larger recent follow up study, respiratory symptoms in over 500 children were classified as reflux or non-reflux induced on the basis of the respiratory response to successful antireflux treatment. Despite the inherent difficulties in a retrospective analysis of this sort, and the recognition that reflux usually improves with time, all the children with respiratory symptoms unrelated to reflux had a mean duration of reflux episode during sleep of less than 3.8 minutes, whereas this was longer in 93% of the group with respiratory disease that was related to reflux. The same group have also examined the usefulness of this index in predicting sudden infant death in infants with gastro-oesophageal reflux. Nearly 500 infants under 6 months of age, of whom over half had a history of apnoea or...
choking, and who had undergone extended oesophageal pH recordings, were followed up and the cause of any deaths during the first year of life elicited. Of the 19 deaths, five were sudden infant deaths or due to a reflux induced arrest in hospital. All five had previously been shown to have pathological reflux, but they had also had prolonged reflux episodes during sleep. Four out of the five infants had also had continuous reflux after an apple juice feed (so called type I reflux), a pattern of reflux associated with only a 21% chance of spontaneous resolution by 18 months. Notably, the incidence of sudden infant death and reflux related deaths was lower after antireflux surgery (0/105) than after medical or no antireflux treatment (5/121). It therefore seems that the frequency of reflux during sleep is much less important than its duration, and may explain why some infants have infrequent but sometimes catastrophic episodes of reflux.

There remains the question of why some infants have such prolonged episodes of sleep reflux. Is there for example, an underlying difference in their sleep or in their ability to be roused by oesophageal acidification? Sondheimer and Hodges have addressed this issue in infants with apnoea or chronic lung disease and were unable to show any differences in the pattern on electroencephalography during sleep between those infants with and without reflux.

What can we conclude? Gastro-oesophageal reflux is certainly common in infants with ALTE and should be sought in them all, using extended oesophageal pH monitoring. Analysis should be directed at determining the duration of reflux episodes during sleep, rather than just relying upon more conventional indices such as the reflux index (percent of total observation time during which pH is less than 4). When found, reflux should be energetically treated with posturing, feed thickening, and cisapride, and oesophageal pH studies should be repeated to determine whether reflux is being prevented. In those infants who fail to respond, my threshold for surgical referral is now low, particularly as some infants will die within days of stopping medical treatment.

Gastro-oesophageal reflux and apnoea in the preterm infant

Reflux in the preterm infant has been incriminated in apnoea, pulmonary aspiration, and bronchopulmonary dysplasia, although accurate data on the incidence and severity of reflux in this population have not been available until recently. It is now clear that gastro-oesophageal reflux is common, and in some infants may be prolonged. Nursing care is a notable precipitating factor and reflux is worsened by the administration of xanthines. In more mature, albeit prematurely born neonates, there does not appear to be a clear association between reflux and apnoeas. Nevertheless, in preterm infants there is a subgroup with non-obstructive, xanthine resistant apnoeas in whom reflux is particularly severe, and in whom treatment of reflux with posturing and feed thickening is associated with resolution of apnoeic symptoms. The mechanism of this association remains obscure and the laryngeal chemoreflex as well as lower oesophageal acidification may be important. However, the observation that resolution of apnoea does not occur as soon as reflux is controlled, but takes place over 48 hours, suggests that a vagally mediated reflex secondary to stimulation of laryngeal chemoreceptors by regurgitated milk is unlikely. It is possible that severe gastro-oesophageal reflux promotes apnoea by a vagally mediated reflex induced by oesophagitis and abnormal oesophageal motility. Preterm infants are said to be at particularly high risk of gastro-oesophageal reflux and pulmonary aspiration during intermittent positive pressure ventilation. Over one third of neonatal units in the UK avoid milk feeds during ventilation. It seems likely that these risks may have been overestimated and that ventilation actually reduces rather than promotes reflux. The use of positive end expiratory pressure and a consequent decrease in the reflux-promoting pressure gradient across the gastro-oesophageal junction may be important in this respect.

Gastro-oesophageal reflux in children with central nervous system disease

Feeding difficulties, vomiting, and recurrent chest infections associated with poor growth and nutrition are common in children with central nervous system disorders, particularly cerebral palsy. It is increasingly recognised that gastro-oesophageal reflux plays an important part in generating many of these symptoms even though vomiting may be minimal. Using barium studies, Abrahams and Burkitt first reported a 75% incidence of reflux in a small group of children and adolescents with severe spastic cerebral palsy. More recently, extended lower oesophageal pH monitoring has confirmed this association. In some children gastro-oesophageal reflux may be the presenting symptom and will appear before the onset of overt neurological disorder. In others, neurological diseases is apparent rather than real, and dystonic posturing, sometimes gross, is cured by effective antireflux surgery (Sandifer’s syndrome).

Oesophageal motor dysfunction is common in children with psychomotor retardation. Lower oesophageal sphincter pressure is often low and peristalsis tends to be weak and disorganised. Oesophagitis is common and may further contribute to oesophageal dysmotility, as well as cause severe anaemia. For this reason, oesophagoscopy is always worthwhile when oesophageal pH monitoring indicates severe reflux or when there is an iron deficiency anaemia. These children require energetic treatment of their reflux. It can cause severe pain, which in older patients is often bad enough to be confused with myocardial infarction. Medical treatment is often of limited value in these patients, presumably because of a primary disturbance in lower oesophageal acid clearance; in contrast to neurologically normal children, cisapride is disappointing. Antireflux surgery therefore plays an important part, particularly in children with severe oesophagitis or other intractable complications. Many children will require preoperative nutritional support as profound protein energy malnutrition is common. At the Children’s Hospital, Birmingham, the median weight for age SD score of children with reflux complicating cerebral palsy was ~2.8, and nearly two thirds of the children had triceps skinfold thickness less than the 5th centile (unpublished observations). This may explain the increased perioperative mortality and complications reported in neurologically impaired children undergoing fundoplication. None the less, it is important to point out that this experience has not been universal and other surgeons report zero mortality and very few complications. Postoperatively, weight gain increases and time spent in hospital is reduced; the operation is highly popular with parents.

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Excitatory amino acid neurotoxicity—a broader horizon for cerebral protection?

Substantial experimental evidence accumulated over the past decade indicates that an endogenous mechanism of toxicity, which results in a selective neuronal lesion more severe in dendirites than in axons (with sparing of glia), may be significant in the process of neuronal degeneration seen after brief neurological insults. Much of the evidence has been pharmacological with protection from the development of morphological neuronal injury by the use of antagonists acting specifically at the glutamate family of neuronal receptors.1 2 The powerful protective effects of these antagonists are potentially of great clinical significance, and could have a role in the treatment of cerebral ischaemia, profound hypoglycaemia, and status epilepticus. In the immature brain, however, the potential usefulness of these agents may be precluded by their adverse effects on behaviour and brain development, because of the importance of excitatory neurotransmission in neuronal outgrowth, plasticity, and cell interaction.3 Despite such a potential limitation for treatment, an understanding of the mechanism of excitatory amino acid neurotoxicity takes us significantly closer to conceptualising the process of neuronal death induced by acute insults, which must be central to any cerebral protective measures.

The 'excitotoxic' hypothesis

In its simplest form the so called 'excitotoxic' hypothesis of neuronal injury proposes that glutamate or other related endogenous excitatory neurotransmitters become toxic in their interaction with glutamate receptors, resulting in a cascade of intracellular events that culminate in neuronal death.4-8 What makes an endogenous transmitter (which is normally released into and cleared from the synaptic cleft) become a neurotoxin is still a matter of much speculation, but these events may be attributable to:

1. An excessive build up of extracellular glutamate because of abnormal neurotransmitter release, or abnormal uptake by neurons and glia;
2. Abnormal glutamate receptor activation because of abnormal postsynaptic sensitivity;
3. Abnormal induction and amplification of intracellular cytotoxic events.

Glutamate receptors

There is evidence for multiple subtypes of excitatory neurotransmitter receptors, which are commonly called glutamate receptors, as glutamates is the most widely accepted endogenous excitatory neurotransmitter. The glutamate receptors can be divided into three groups. There are two classes which possess an intrinsic ion channel, called ionotropic receptors. These are the N-methyl-d-aspartate (NMDA) receptor and the non-NMDA, kainate/quisqualate receptor, which are presumed to be large, multisubunit integral membrane protein complexes, which possess receptor binding sites with a central ion channel. The third class of receptor is the metabotropic glutamate receptor, which instead of possessing an intrinsic ion channel exerts its action through second messenger systems by activation of a G-protein.

An understanding of the extent to which these glutamate receptor subtypes contribute to the neuronal injury induced by acute cerebral insults has been facilitated by experimental...
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