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Chapter 91

Syncopes and other paroxysmal events

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INTRODUCTION

This chapter outlines some important paroxysmal events of infancy and childhood that are not epilepsy. The discussion on syncope predominates because syncopes are so frequent and so often misdiagnosed. However, conditions such as narcolepsy and hyperekplexia are qualitatively as important.

SYNCOPES

Syncopes are so common in childhood that pediatric neurologists or neuropediatricians should be very familiar with their symptomatology (Stephenson, 1990; Lempert, 1996). In part this is so that syncopes may be distinguished from epileptic seizures but also because the syncopes may need specific management. It should not be necessary to say that syncope does not mean swooning or lax hypotonic fainting – syncopes may be dramatic convulsive events sufficient to make a parent or a witness say, "That's a seizure, isn't it?" (Stephenson, 2001).

Neurally mediated syncopes

In adults neurally mediated syncope means neurocardiogenic or vasovagal syncope. In childhood the term has a broader meaning, but includes vasovagal syncope of the classical type.

Mature vasovagal syncope

This is the best known of the syncopes and worth discussing in detail because most of the features are also seen in the toddler and infantile syncopes discussed below.

Presentation

As in all syncopes (and indeed in many of the nonepileptic paroxysmal disorders) one expects there to be a provocation or stimulus, and often a typical setting. Prolonged standing in a warm or oppressive environment is one scenario but equally syncopagenic are unpleasant stimuli such as pain, injury, or the sight of blood. Some triggers are so specific as to allow a clinical diagnosis without any investigations; these include venepuncture, ear piercing, and hair grooming, whereas if domestic bathing of an infant is the trigger one may say with confidence that the diagnosis is *not* syncope (Nechay and Stephenson, 2008).

If old enough, a child will recollect an aura of graying out of vision and alteration in the quality of sounds. Hallucinations are commonly experienced though not volunteered without questioning. Similar altered sensations and dream-like hallucinations (sometimes with out-of-body experiences) may also be experienced at the end of the syncope.

Observers usually notice a change in the child's skin, not necessarily to a pale color, sometimes to what is described as green, before the child falls.

If standing, the child may just crumple, falling without increased tone, but stiff falls also occur. Whichever way the child falls, atonic or hypertonic, various combinations of extensor stiffening and (nonepileptic) spasms are the norm, the spasms often being vigorous enough to be described as jerks. These jerks have been described as myoclonic but are not as short as epileptic myoclonus and have more the duration of epileptic spasms. Jerking is almost always *arrhythmic* without the rhythmic or semi-rhythmic quality that characterizes clonic epileptic seizures. This motor activity in syncope is almost universal in experimental syncopes, but is much less often observed in practice, perhaps because the usual "convulsive" aspect is mild or fleeting.

More complex movements in the form of automatisms are less common than elementary movements, but are not rare.

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Abnormal eye movements are even less well observed in everyday practice than limb movements, despite the fact that the eyes are usually open. Most common are tonic upward deviation and down-beat nystagmus, but horizontal lateral deviation may occur, these ocular versions sometimes associated with tonic posturing resembling the neonatal asymmetrical tonic neck reflex.

Urinary incontinence occurs frequently, in boys as well as girls, and is a distressing complication.

The duration of the whole episode is commonly only 1 minute, rarely 2, and then the child is able to respond in some way, although pallor and fatigue and unpleasant sensations and feelings may last for hours.

Syncope during exercise may be vasovagal, but exertional syncope is a warning to check for potentially lethal cardiac arrhythmias (long QT in particular – see below). Other red flag scenarios are syncope on emotional exertion (such as being chased by a bull), while swimming, or at the sound of an alarm clock; see long QT discussion below.

Investigations

It is wise to obtain a 12-lead ECG if the history is not typical, but an EEG is *not* indicated. One should bear in mind that 2% of normal children may have discharges such as rolandic sharp waves and that finding such an "abnormality" may lead to diagnostic confusion. Neither is ocular compression (OC) during EEG justified except in the most exceptional circumstances (Stephenson, 2008).

It is our opinion that a head-up tilt test is worth arranging only if it is important to reproduce the syncope. A "positive" result means both that it feels the same to the child as the usual episodes and that the parent observing (a parent must be present) recognizes the event as identical to natural attacks. Head-up tilt should also be monitored by video, with EEG, ECG, and continuous non-invasive blood pressure – and continuous trans-cranial Doppler and pCO_2 – monitoring if pseudo-syncope is in the differential, so the test should not be requested lightly.

Serum ferritin measurement is justified because low iron stores predispose to neurally mediated syncope in children (and hemoglobin levels might be tested at the same time) (Jarjour and Jarjour, 2008).

Management

Minimal investigations (except ECG and ferritin) and sympathetic informed reassurance should be adequate in most cases. When necessary, physical countermeasures (muscle tensing, leg crossing) are harmless, free-of-charge, evidence-based methods of treatment (Kuriachan et al., 2008).

Reflex asystolic syncope

RAS was coined as the acronym for reflex anoxic seizures (Stephenson, 1978) but reflex asystolic syncope is a better translation. Whereas mature vasovagal syncope is a combination of vasodepressor and cardiovagal elements, RAS seems purely a cardiovagal syncope. Much confusion has been generated by the habit of calling RAS pallid breath-holding attacks, when "breath-holding" is not involved. If episodes continue from infancy into older childhood and adolescence (or indeed adulthood) they are called vasovagal syncope.

There is almost always a provocation for RAS. Typically it is an unexpected stimulus such as a bump to the head or to the face, often minimal.

At onset there may be a gasp during the short latency gap between the head bump and the motor manifestations. Extensor spasms, sometimes with double extension, are often but not always associated with facial pallor and perioral cyanosis. At the conclusion, as the toddler awakes, there may be a beetroot flush that reflects reperfusion.

A 12-lead ECG is indicated unless the history is absolutely typical, but beware the over-diagnosis of LQT syndromes (Taggart et al., 2007). An EEG is *not* indicated (Stephenson, 2007).

The only place for an EEG examination today is when combined with ECG and ocular compression (OC) in order to *reproduce an episode of RAS* in the presence of the parents (Stephenson, 2008). Simultaneous video is desirable in this circumstance to allow further review with the family afterwards. OC is indicated only for the purpose of reproducing an episode (see also discussion of anoxic-epileptic seizure below). Semi-long-term lightweight ECG loop recording to capture an episode at home is worthwhile before any medication is used (see below) or if presumed RAS is so frequent or severe that cardiac pacing is an option. Implantable ECG loop recorders are indicated only if the presumed RAS episodes are so frequent or severe that cardiac pacing is likely.

Management

Sympathetic informed reassurance should be adequate in most cases. Explaining that the heart has re-started before the end of the motor event is helpful. So is an explanation of negative feedback in lay terms: the heart stops because the vagus nerve discharges excessively, but when the vagal nuclei in the brainstem receive no blood supply the vagus stops inhibiting the heart and it starts again, *always*.

Cardiac pacing is only rarely needed when RAS episodes have extreme adverse effects on the child's life

(McLeod et al., 1999). Finding cardiac asystole of 20–30 seconds is *not* in itself an indication for pacing.

Prolonged expiratory apnea (cyanotic "breath-holding")

Prolonged expiratory apnea (PEA) (Southall et al., 1985) is the preferred term for what have been called cyanotic infantile syncope, cyanotic breath-holding, blue breath-holding, or just breath-holding spells (Breningstall, 1996). In some countries they are known as affective or psycho-affective respiratory attacks, and by Francophones as *spasmes du sanglot*. Onset may be as early as the neonatal period. Offset is commonly before school age, but if episodes occur at older ages then, as with RAS, they are called vasovagal syncope – suggesting a common mechanism. In the opinion of this author, breath-holding spells is a misnomer and should be applied only when there is true breath-holding, as in compulsive Valsalva maneuvers (see below).

Annoyance or frustration might be more provocative of PEA than pain but data are difficult to find. Rapidly repeated expiratory grunts ending in full expiration are followed promptly by deep cyanosis and tonic, and often opisthotonic, posturing of a decerebrate type. An inspiratory groan then precedes relaxation, and crying occurs when consciousness returns.

No investigations are indicated if the infant or child is neurodevelopmentally normal, except perhaps for estimation of hemoglobin and ferritin level.

A rare but important differential diagnosis is intentional suffocation by the mother (rarely the father), that is to say imposed upper airways obstruction (IUAO) (Southall et al., 1997). IUAO begins only in the presence of the parent, but may be shown to other family members, nurses, and doctors at the stage when resuscitation is required (Stephenson, 1990).

Management

Explanation and informed reassurance are what is on offer. Before saying to the parents that the episodes are "only breath-holding spells," it is worth remembering that a published study has found "breath-holding spells" to be more stressful for a family than having a young child with epilepsy (Mattie-Luksic et al., 2000). However, clinical experience is that most families are happy that the doctor has confirmed their thoughts about the good prognosis.

Mixed or indeterminate early childhood syncopes

Sometimes it is not easy to tell whether an infant, toddler, or child has RAS or PEA or some combination of the two mechanisms. If such episodes are by chance or design recorded on EEG with ECG and video then one may see both the rapid notch artefact of expiratory grunting and also the cardiac asystole typical of RAS. *If* young children really did hold their breath in this clinical scenario, the overlap in this mixed group would be a justification for using "breath-holding spells" in an all-encompassing manner.

Neonatal hyperekplexia

Severe apneic syncopes are a feature of neonatal hyperekplexia (sometimes misspelt hyperexplexia). These life-threatening syncopes are usually but not always accompanied by hypertonia, giving the so-called stiff-baby syndrome. The infant shows a combination of excessive auditory startle and a head-retraction reflex on tapping the tip of the nose.

Syncopes begin within a day or two of birth; triggers may not be obvious but often include the domestic bath. A rapid-fire staccato cry turns to silence as the infant stiffens in prolonged apnea and becomes cyanosed. Motor anoxic seizures may then be seen with nonepileptic spasms and urination (Rees et al., 2006).

Ictal EEG/ECG is characteristic, and possibly specific. Repetitive high-voltage EMG "spikes" (compound action potentials) are seen on all EEG channels that overlie scalp muscle and on the ECG channel (and on the deltoid EMG if sampled) at a rate of about 8–30 Hz. Underlying this the EEG background slows and becomes isoelectric, while the ECG shows first tachycardia then bradycardia that may be junctional with absent P waves.

Genetic analysis will reveal either mutations in the gene for the alpha-1 subunit of the glycine receptor *GLRA1* or more likely in the gene for the presynaptic glycine transporter GlyT2 (*SLC6A5*).

Management

Parents and staff should be taught the simple Vigevano maneuver (Vigevano et al., 1989), forced flexion of the head and legs towards each other, curling the baby up into a ball. This usually stops a profound apnea from developing.

Prophylactic oral clonazepam is given in whatever dose is both tolerable and effective. In some children with GlyT2 mutations, the clonazepam can be discontinued early, while with GLRA1 mutations clonazepam usually needs to be given life-long.

Paroxysmal extreme pain disorder

Paroxysmal extreme pain disorder (PEPD) (Fertleman et al., 2007) is a rare and terrible condition (previously called familial rectal pain) now known to be due to

mutations in the sodium channel subunit *SCN9A* that is expressed both in nociceptive neurons in the dorsal root ganglia and in the sympathetic ganglia.

Onset is in the neonatal period, commonly on day 1. Episodes begin without obvious precipitation or in response to perineal toilet or to the act of defecation. Flushing of the skin is a constant early feature, usually with harlequin change, in particular redness on one side of the face and pallor on the other. With the flush there may be a glazed expression, tonic stiffening, apnea, and alterations in heart rate and rhythm. Occasionally cardiac asystole is seen, but the severe syncopes are not prevented by cardiac pacing.

With age the characteristics of attacks change, and extreme pain becomes more obviously dominant, with the site of maximum pain varying between the rectogenital area, the jaw, and the eyes.

Management

Very detailed counseling by an informed physician is necessary. If the daily dose is large enough, carbamazepine helps all patients, but it may not be sufficient to abolish pain.

Compulsive Valsalva

Although children affected by this habit are rarely reported, in an individual child compulsive Valsalva maneuvers constitute the most frequent of all syncopes. Autistic spectrum disorder or "asymbolic" mental retardation underlie this habitual behavior. Frequent episodes recur without provocation in a child with obsessive traits.

Hyperventilation usually precedes the strong Valsalva maneuver that is recognized by approximately 11 seconds of silence during the respiratory arrest that is a true "breath-hold." At the conclusion of the "breath-hold" there may be atonia or more often a tonic extension with upper limbs extended, elevated, and abducted (Stephenson, 2001).

Video with audio may be sufficient for diagnosis, if attention is paid to the lack of breathing sounds during the "breath-hold." EEG/ECG will document the typical changes if an episode is recorded, with ECG showing a combination of tachycardia and reduction of QRS amplitude by about 50% followed by – after about 10 seconds – rebound bradycardia, and a burst of EEG slow activity (Gastaut et al., 1987).

Management

Management is difficult. No evidence base exists for any particular treatment. Fenfluramine, naltrexone, and the use of a wrestler's belt have been reported to be effective, at least in the short term.

Stretch syncope of adolescence

Adolescents may self-induce syncope by stretching and extending the neck. How much a Valsalva maneuver contributes is debatable (Thijs et al., 2007). Diagnosis is by clinical history, investigations are not required, and management is "be careful when you stretch!"

Long QT syndromes

The existence of potentially lethal cardiac syncopes masquerading as epilepsy underlines the importance of recognizing nonepileptic seizures. Although practitioners need to be wary of diagnostic miscues, it is better to be safe than sorry.

Long QT syndromes (LQTS) (Crotti et al., 2008) are by far the most common of the cardiac conduction disorders that may present as "seizures." A provocation of such syncopes is usual but not constant. Exercise, especially stressful exercise, and high emotion are well known precipitants, as is swimming in LQT1 and a sudden sound such as an alarm clock in LQT2. Syncopes may also occur in sleep.

"Seizure" is how events will be described, as the syncopes are commonly convulsive (but nonepileptic) with minimal warning and with prominent motor components. Thus they resemble RAS, except for different provocations.

Pre-syncope, swooning, and gentle syncopes after a prominent aura are not expected.

It is important to try *not* to do an EEG! (Such examples may only be anecdotes, but once one has seen preventable sudden death in a child misdiagnosed as having epilepsy because of frequent central spikes on EEG one hates to imagine that happening again.) If – for the wrong reasons – an EEG has already been done, the ECG channel should have been assessed by the Gospe method for long QTc (Gospe and Gabor, 1990). Once the ECG has been recorded it is important that the QTc should be measured by a human and not just by a computer.

Genetic studies are best left to the cardiologists and the geneticists.

Apneic syncope of congenital myasthenia

Apneas of neuromuscular origin are not usually thought of as syncopes but if they are not thought of in this way then serious treatable disorders may be overlooked (Kinali et al., 2008).

Congenital myasthenia may present with severe life-threatening apneas and consequent respiratory syncopes without obvious weakness.

Edrophonium testing may not be clearcut, and a trial of pyridostigmine may be necessary. Stimulation

single-fiber electromyography (sSFEMG) of the orbicularis oculi muscle is becoming the best diagnostic choice in children. Genetic studies at a myasthenia reference laboratory will be in order.

Management is usually by pyridostigmine but the overall care of a myasthenic infant is necessary until remission occurs.

Anoxic-epileptic seizures

When a syncope (an anoxic seizure) triggers an epileptic seizure this combination is called an anoxic-epileptic seizure (AES) (Horrocks et al., 2005).

The syncopal trigger may be any of the types of neurally mediated syncope related to vasovagal syncope, that is, RAS, PEA, mixed syncopes, and the syncopes of compulsive Valsalvas.

The epileptic component is usually clonic, but not completely generalized. Conjugate lateral eye deviations seem common and the young child may appear as if trying to speak during the rhythmic or semirhythmic jerks. Clonic status epilepticus is not rare as part of AES.

Absence epileptic seizures are a less frequently reported component that may become absence status.

Management

The management of the syncopal aspect is as indicated under vasovagal syncopes, RAS, PEA and compulsive Valsalva, as above. In general, the frequency of such syncopes cannot be influenced by treatment, except perhaps by iron supplementation.

Alternatives for managing the epileptic component include rescue medication by a benzodiazepine and prophylactic valproate or carbamazepine, if the low risks of these antiepileptic medications are agreed by family and doctor to be justified.

One should counsel that epilepsy – that is, unprovoked epileptic seizures – is not an expected outcome.

NARCOLEPSY AND CATAPLEXY

Narcolepsy–cataplexy

Narcolepsy with its attendant cataplexy is not rare in childhood but it is likely that many cases are falsely diagnosed as epilepsy and missed for years (Macleod et al., 2005). The characteristics are well known – excessive daytime sleepiness, hallucinations especially hypnagogic, sleep paralysis, REM behavior disorder, and cataplexy – but none of these symptoms may be volunteered and instead the child presents with learning and/or behavioral difficulty, attention deficit, or conduct disorder (Dorris et al., 2008).

In cataplexy, laughter or a joke or similar intense emotion leads to sudden loss of antigravity tone that begins in the face and neck and progresses in a cephalocaudal direction. First the face droops, the head falls forward and the child crumples to the floor, immobile but fully conscious. Video recording at home or in hospital is an extremely helpful investigation in the recognition of cataplexy.

It is usual also to suggest: HLA typing for DQB1*0602, overnight polysomnography, multiple sleep latency test, and if possible CSF hypocretin. CSF hypocretin has a high sensitivity but a lower specificity; in other conditions with cataplexy CSF hypocretin may be low.

Management

Aside from medications to deal with the narcolepsy and the cataplexy, affected children need neuropsychological evaluation, counseling, and long-term psychological and school-related support.

Cataplexy in other conditions

While narcolepsy is by far the most common association, cataplexy is not rare in Niemann–Pick type C. Narcolepsy may also be seen as an autosomal dominant trait, and in syndromes such as Prader–Willi. About 25% of those with Coffin–Lowry syndrome have falls in response to startling sounds, and sometimes true cataplexy as well. A very rare cause of cataplexy is the paraneoplastic hypothalamic syndrome secondary to an occult neural crest tumor.

SHUDDERING, BENIGN SPASMS, GRATIFICATION, TONIC UP-GAZE

A motley collection of benign paroxysmal motor phenomena of infancy remain to be discussed. The relationships between several of them are discussed in Caraballo et al. (2009).

Shuddering

Isolated but sometimes very frequently repeated episodes of transient shudder seem to combine the features of brief tremor and spasm, that is, brief tonic activity.

Benign nonepileptic infantile spasms/benign myoclonus of early infancy

These names are interchangeable but benign nonepileptic spasms is preferred by this author. The characteristic appearance of clusters of repetitive flexions leads to the misdiagnosis of epileptic infantile spasms or West syndrome. Individual episodes may be indistinguishable from shuddering.

Infantile masturbation/gratification

Episodes of repetitive thigh adduction may simulate epilepsy or dystonia. Cessation with distraction is usual (Nechay et al., 2004).

Benign tonic up-gaze

Paroxysmal tonic up-gaze now seems a heterogeneous condition (Caraballo et al., 2009) that does not always have a favorable outcome (Hayman et al., 1998) and, unlike the three conditions previously outlined, may include "organic" conditions such as channelopathies and dopa-responsive disorders.

CONCLUSION

Paroxysmal disorders other than epilepsy are very frequent in infants and children and it behoves pediatric neurologists to be well familiar with their protean manifestations.

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