Startles, jumps and fits

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INTRODUCTION

We are all personally familiar with the startle response – the abrupt ‘start’ or ‘jump’ in response to sudden unexpected stimuli, like a loud noise. This startle is a nonsuppressible reflex, which alerts us to abrupt changes in our environment that may threaten our safety. It is a reflex with survival value. But, if excessive or too easily triggered, it can interfere with daily functioning, or cause falls or injuries, and it is then a pathological response. The startle reflex is thought to be mediated at the level of the midbrain or below, because it is still elicited in decerebrate animals (Forbes & Sherrington 1914). The intensity of the startle reflex in humans varies between individuals and is increased by anxiety, fatigue or emotion (consider your response to a door slamming as you are watching a late night horror movie).

Pathological startle syndromes can be divided into (Fig. 1):
- Primary startle syndromes (startle disease and startle epilepsy)
- Startle secondary to other pathologies
- Psychogenic startle
- The culturally linked startle syndromes

Fig. 1. A framework for classifying the startle syndromes

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Startles, jumps, falls and fits
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This review will provide an overview of the different types of startle syndromes, which are uncommon but interesting - and potentially treatable. But not everything that jumps is startle disease.

### STARTLE DISEASE (HYPEREKPLEXIA)

Hyperekplexia is uncommon (the exact prevalence is unknown) and is one of the few treatable neurogenetic disorders. The diagnosis is usually straightforward - once one is aware of the clinical features. Early diagnosis and treatment can prevent much of the morbidity and mortality. Recognition of the condition is also important because affected families can be referred for genetic counselling.

#### Illustrative case history

A 26-year-old right-handed man was seen in the neurology clinic, having suffered with ‘drop attacks’ since childhood. His mother had become concerned about his frequent falls at the age of six, particularly as he made no obvious attempt to save himself and had sustained a number of facial injuries. She said he did not seem to tumble and there was no loss of consciousness, but she had noticed that loud noises often precipitated a fall. He had been seen at the age of three and diagnosed with a spastic diplegia and equinovarus deformity of the right foot. At the time of review in the adult clinic, neurological examination was entirely normal. A detailed family history revealed that a number of other family members were also affected (Fig. 2) and the patient reported that his 2-year-old daughter had been ‘stiff’ when she was born. She was just starting to walk and he was concerned by the fact that she also seemed to fall frequently.

#### Inheritance and pathophysiology

Hyperekplexia is usually inherited in an autosomal dominant fashion (as in the case history above), although there have been reports of recessive inheritance, and sporadic cases. The genetic defect is linked to chromosome 5 and different mutations in the inhibitory glycine receptor (GLRA1) gene have been identified in a number of affected families (Shiang et al. 1993). Mutations of GLRA1 uncouple ligand binding and chloride channel function of the inhibitory glycine receptor. The result is thought to be an increase in excitability of the pontomedullary reticular neurons and abnormal spinal inhibition.

Interestingly, hyperekplexia is known in animals, which provide experimental models for the condition. (Healey et al. 2002) described a bovine form of myoclonus (with an accompanying video supplement), which closely resembles human hyperekplexia. Affected animals have myoclonic jerks in response to sensory stimuli and heightened responsiveness. Lifting them causes excessive stiffness and extensor spasm, but with no loss of consciousness, and recovery is rapid. This, too, is the result of a mutation in the glycine receptor α-subunit leading to a failure of glycine-mediated inhibitory neurotransmission in the spinal cord and brainstem. There are also three strains of mice (spastic, spasmodic and oscillator) that have a phenotype resembling hyperekplexia, all of which have a genetic defect involving glycine receptors (Ryan et al. 1994; Kingsmore et al. 1994).

#### Clinical features

Human hyperekplexia often appears in the neonatal period. Affected neonates are diffusely hypertonic and hyperreflexic and have an exaggerated startle response to noise and handling, usually head retraction and tonic flexion of the body. Hernia may be associated due to raised intra-abdominal pressure. Startle during feeding can result in aspiration, apnoea and sudden death – it is therefore important that affected neonates are monitored closely. Muscle stiffness tends to settle during the first year, but walking may be delayed due to fear of falling. Children may crawl around on their knees or bottoms before adopting a normal gait. Parents may also notice clonic jerking, particularly of the legs, during sleep. This is not associated with epileptiform discharges on the EEG and does not respond to antiepileptic drugs.

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**Fig. 2.** The family history of the illustrated case, clearly showing autosomal dominant transmission

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Why does an adult neurologist need to be aware of the paediatric manifestations of this condition? Firstly, paediatric patients with hyperekplexia may be referred to adult clinics in adolescence. Secondly, it is important to ask about these clinical features in patients’ children when taking the family history. Thirdly, in patients with established hyperekplexia, it is important to alert them to the possibility of neonatal problems if they are planning a family, particularly the need for vigilance during feeding and apnoea monitoring at night.

Adults with untreated hyperekplexia continue to have excessive startle and run the risk of severe injury from frequent falls. In response to a sudden, unexpected stimulus (usually noise, although attacks can be precipitated by sudden tactile stimuli), the patient suddenly stiffens and then falls to the floor without loss of consciousness. The arms are held rigidly by the sides and the patients are unable to save themselves. Falls can result in severe facial lacerations, skull or limb fractures, and some patients may even take to a wheelchair to avoid falling.

The demonstration of other affected members in the family can be difficult because major and minor forms may coexist in the same family. The major form of hyperekplexia is associated with generalized hypertonia in the first year of life, exaggerated startle and falls, whereas in the minor form, exaggerated startle and hypnic jerks are the only features (Suhren et al. 1966).

Neurological examination in adults is generally entirely normal. Affected neonates may show hypertonicity, and tapping their nose may precipitate their exaggerated startle in the form of sudden head retraction and tonic flexion of the body. This excessive backward jerking of the head in response to tapping the nose or forehead persists into adulthood (Shahar & Raviv 2004).

Investigation
Atypical features in the history or examination are reasons for magnetic resonance imaging (MRI) of the brain to rule out central nervous system causes of startle (Fig. 1 and below). EEG correlates of startle have been described (Suhren et al. 1966; Gastaut 1967): centroparietal vertex spikes followed by slow waves and desynchronization of background activity lasting a few seconds. However, the diagnosis still remains largely clinical.

Treatment
Hyperekplexia is one of the few eminently treatable neurogenetic disorders. Clonazepam will reduce the exaggerated startle response and therefore the risk of falling (Andermann et al. 1989; Dubowitz et al. 1992). However, there is little information on the optimum dose or duration of treatment. In the paediatric literature, 9 severely affected infants were treated with 0.2 mg/kg/day of clonazepam and 7 showed complete recovery allowing treatment to be discontinued after 6 months (Shahar & Raviv 2004). Ryan et al. treated 16 patients in a large kindred with clonazepam and found a dramatic and sustained response (Ryan et al. 1992). Sedation may occur as an adverse effect and one case report described the effectiveness of clobazam (0.25–0.3 mg/kg/day) in two affected infants unable to tolerate clonazepam (Stewart et al. 2002). There is some evidence to suggest that valproate and piracetam may also be helpful (Dooley & Andermann 1989; Saenz-Lopez et al. 1984).

SECONDARY STARTLE DISORDERS
Exaggerated startle has been reported in association with brainstem pathology such as multiple sclerosis (Ruprecht et al. 2002), vascular anomalies (Gambardella et al. 1999), paraneoplastic brainstem encephalitis, subacute viral encephalomyelitis, brainstem haemorrhage and sarcoidosis (Matsumoto et al. 1994). It can occur with cervicomедullary compression (Salvi et al. 2000) (Matsumoto et al. 1994), and in one case improved after decompressive surgery (Winston 1983). Ischaemic lesions such as posterior thalamic artery occlusion (Fariello et al. 1983) or pontine infarction may result in hyperekplexia, possibly as a result of disinhibition of the normal startle reflex. Hyperekplexia may also occur as a component of generalized tetanus (Warren et al. 2003), after head injury, or in association with postanoxic encephalopathy (Joachim et al. 1997).

PSYCHOGENIC STARTLE RESPONSES
Psychogenic startle has been described when stimulus-induced jerking occurs as part of an apparent myoclonus or pathological startle syndrome (Thompson et al. 1992). In two of the five patients described, jerking followed minor injuries to the head and neck; a further two patients had a background of neurological illness. Clinical suspicion of a psychogenic origin was aroused when close observation of the patients revealed that their symptoms were not typical of either myoclonus or hyperekplexia. In three of the patients in whom jerking occurred in response to sudden stimuli, there had been no falls. In two of the patients, the pattern of jerks was altered when the patient was distracted and in one, the exaggerated startle occurred in response to loud noises on

FEATURES OF STARTLE DISEASE (HYPEREKPLEXIA)
• Hyperekplexia is a treatable neurogenetic condition
• It is usually inherited in an autosomal dominant fashion and is one of the channelopathies
• Exaggerated startle causes falls which can result in severe injury
• Affected neonates run the risk of aspiration and apnoea due to startle responses during feeding, and they require close monitoring
• Early and accurate diagnosis significantly improves quality of life and reduces risk of injury
• Liaison with obstetric and paediatric teams can raise awareness of the particular risks that are associated with delivery and the neonatal period
• Hyperkplexia responds well to clonazepam, which is usually well tolerated and does not lose efficacy with time
• Affected patients should have genetic counselling
• Unexpected features in the history or examination should prompt a search for underlying CNS pathology
the ward, but not when walking in the street in the company of medical staff.

Neurophysiological studies provided further evidence that the abnormal movements were not secondary to hyperekplexia or myoclonus. The latencies to onset of jerking were long and variable and there was a variable pattern of muscle recruitment. The responses also tended to habituate. The authors compared these responses to those of normal volunteers, asked to imitate a generalized jerk in response to sensory or auditory stimuli. The patients with psychogenic jerks had longer reaction times than the fastest voluntary reaction time of normal subjects and a similar pattern of muscle recruitment. In one patient, the jerks resolved when the possibility of a psychogenic origin was discussed with her. The diagnosis of psychogenic movement disorders can be difficult but simple neurophysiological testing is helpful.

CULTURALLY LINKED STARTLE SYNDROMES

The culturally linked startle syndromes are interesting and remain controversial (Joseph et al. 1992). The 'Jumping Frenchmen of Maine' and Lâtah have been the most extensively studied, but other similar disorders have been described worldwide. These disorders are characterized by pathological startle associated with echolalia, echopraxia, coprolalia and automatic obedience behaviour, and were in fact described by Gilles de la Tourette in 1885.

The 'Jumping Frenchmen of Maine'

The 'Jumping Frenchmen of Maine' were first described in the late 19th century, when George Beard came across a group of men with an abnormal startle response consisting of jumping, raising their arms, hitting, vocalization and repetition of sentences (Anon 1980). This same phenomenon was also seen in a group of lumberjacks who were teased by their colleagues in lumber camps. In both cases, the men were noted to be excessively ticklish. The enhanced startle in the lumberjacks was enhanced by the attention it attracted and was felt to be a conditioned response because when they left the environment in which stimuli and positive reinforcement were frequent their responses became less intense and less complex (Joseph et al. 1992).

Lâtah

Lâtah has been recognized in Malaysia since the fifteenth century, and by contrast affects females more than males. Affected females are timid and passive, but the clinical features are very similar to 'jumping'. In addition to exaggerated startle, the women have automatic obedience behaviour, which can range from dancing to more bizarre behaviour, sometimes mimicking sexual actions (Simons 1996). The female preponderance in Lâtah may be because both men and women preferred to startle women because they could do so with impunity (Simons 1996), not always the case when Lâtah men were startled! There has been some controversy as to whether Lâtah is an organic disorder because people with Lâtah have been observed exaggerating their dysfunction either to attract attention or to have an excuse for behaviour that may otherwise be culturally unacceptable.

Bartholomew (1994) described 37 cases of Lâtah from his own extended Malay family, 33 of whom had coprolalia in response to startle, and 4 had bizarre behaviour and automatic obedience for up to 10 min. The first group were categorized as 'habitual' Lâtah and the second group as 'performance' Lâtah. The author hypothesized that the first group constituted a conditioned habit as part of a response to stress and the second group were exhibiting a conscious ritual for social gain (i.e. attention-seeking behaviour).

STARTLE EPILEPSY

Startle provoked seizures are rare but well described. The purpose of this overview is to highlight the distinction between startle disease (hyperekplexia) and startle epilepsy. Startle epilepsy is recognized as a syndrome, but patients with startle-induced seizures are, in fact, a heterogeneous group with variable aetiologies and EEG correlates (Panayiotopoulos 2002). Startle epilepsy is a form of reflex seizure in which startle activates the epileptiform discharge.

Clinical features

Startle epilepsy was originally thought to be rare in those with normal intellect and neurological function. The first description of abnormal startle associated with seizures was by Alajouanine and Gastaut (1955, cited in Anderman et al. 1980). They described...
two types in children with infantile hemiparesis or quadriparesis and diffuse cerebral dysfunction:
- Startle synkinesis, where the weak limb undergoes a 5–10 second tonic contraction, often causing falls
- Startle epilepsy where in addition to startle tonic contraction, there were other clinical or electrophysiological signs of seizure activity

Startle seizures are asymmetrical in 25% of patients. The initial tonic contraction of the paretic limb may spread to the contralateral side and there may be other symptoms such as automatisms, laughter or autonomic manifestations. Seizures are frequent, may progress to status epilepticus and are typically refractory to medical treatment. Spontaneous (non-startle provoked) seizures occur in many patients with startle epilepsy, but are infrequent. Prognosis tends to be poor, particularly for those with severe pre-existing brain damage (Panayiotopoulos 2002). Startle epilepsy has been described in association with Sturge-Weber syndrome.

These days, it has been suggested that startle-provoked seizures may occur more frequently than previously thought in the context of normal neurological function. Manford et al. (1996) described 19 patients with startle epilepsy, 10 of whom had no abnormal neurological signs. There was no difference in seizure frequency, severity or response to treatment between the groups with and without a neurological deficit. Onset was usually in childhood or adolescence, but could occur in adulthood. Seizures tended to be brief but frequent and in most patients evolved into tonic motor activity and asymmetrical posturing. Intercital EEG abnormalities varied within and between patients, but tended to affect the frontal, temporal and central regions. In patients with a hemiparesis, a porencephalic cyst or focal atrophy was seen in the contralateral hemisphere. In a number of patients with normal CT scans, high resolution MRI demonstrated dysplastic brain lesions.

Treatment of startle induced seizures is difficult although some patients respond well to carbamazepine or sodium valproate (Sainz-Lope et al. 1984), and response to lamotrigine has been reported (Faught 1999). Surgery may be considered in patients with focal brain lesions.

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