Self-assessment

Case 1

A 20 month old male was referred to the neurology clinic with concerns regarding his gross motor development and worsening tremors. He sat without support at 6 months, but has never been able to pull to sit or to crawl. He could support his own body weight, but was unable to pull himself up to stand. A tremor has been present since 10 months old, noticeable in his hands and feet, worse when frightened, unwell or uncomfortable, better when relaxed and no suggestion of fatigability.

The pregnancy and delivery were unremarkable. He was otherwise well, with the remainder of his development appropriate for age. There was no relevant family history.

On examination he was thriving. A resting tremor was present with no other cerebellar signs. Cranial nerves were intact. Hypotonia was present, particularly in the lower limbs, hypermobility and proximal weakness; He had a waddling gait and required upper limb support when sitting or standing.

Q.1 What would be the most important next investigation?

A) CK
B) MRI Head
C) Muscle biopsy
D) Genetic studies
E) Lactate

The CK, MRI head, organic and amino acids were normal. The EMG/nerve conduction study showed normal sensory nerve conduction, but a generalised motor neuronopathy indicating an anterior horn cell disease.

Q.2 What is the most likely diagnosis?

A) Polio
B) SMA type 1
C) SMA type 2
D) Charcot Marie Tooth type 1
E) Acquired Myasthenia Gravis
F) Duchenne Muscular Dystrophy

Q.3 With what test would you confirm the diagnosis?

A) Enteroviral PCR
B) Microarray
C) PCR for SMN gene deletion
D) Muscle biopsy
E) PCR for PMP22 mutation

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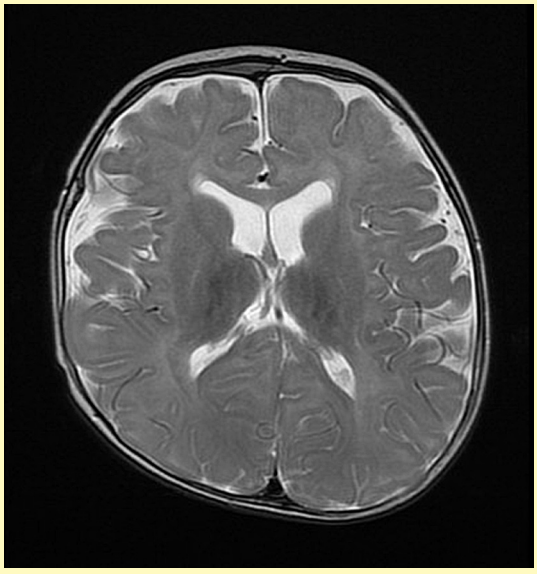
Case 2

A 4 month old male presented to the emergency department with irritability, not tolerating feeds, vomiting and failure to thrive. He was initially investigated for urinary tract infection and had trialled treatment for gastro-oesophageal reflux and cow's milk protein intolerance. There was also concern that he was losing previously acquired skills. He was born at term after an uncomplicated pregnancy and there was no relevant family history.

On examination he was very unsettled and had increased peripheral muscle tone. Fisting and head lag were present and he was not reaching out for toys. The remainder of the examination was normal.

An MRI head showed mildly prominent periventricular spaces and adjacent to this, white matter of high intensity.



A neurometabolic screen generated the following results:

CSF protein	1.35 (High)
CSR lactate and glucose	Normal
Urine glycosaminoglycans	Normal
Urine organic acids	Normal
Ammonia	Normal
Transferrin glycoforms	Normal
Very long chain fatty acids	Normal
Galactocerebrosidase enzyme activity	Low

Q. 1 What is the most likely diagnosis?
A) Hunter disease
B) Gaucher disease
C) Zellweger syndrome
D) Krabbe disease
E) Congenital disorder of glycosylation

Q.2 What is the best treatment option for this boy?
A) Symptom support only
B) Enzyme replacement therapy by life-long, daily, oral medication
C) Dietician advice regarding a methionine restricted diet
D) Research trial recruitment for gene therapy

Q.3 Assuming this was inherited in an autosomal recessive manner, what is the probability of his, otherwise well, 8 year old sister being a carrier?
A) less than 1%
B) 25%
C) 33%
D) 50%
E) 66%
F) 75%

Case 3

A 12 year old male was transferred to a tertiary hospital for a neurology opinion after presenting with a month history of bilateral ptosis and limb weakness. He was otherwise well, with no previous medical problems or family history.

The ptosis used to be better first thing in the morning. Ophthalmoplegia was present on examination together with mild weakness in the upper limbs. Reflexes were preserved. Neurophysiology showed a generalised significant decrement in repetitive stimulation of limb muscles.

Q. 1 What is the most important bedside test to monitor?
A) Oxygen saturations
B) FEV1
C) The time able to raise leg 45 degrees off the bed
D) Degree of ptosis present
E) The ability to count to 50 at speed

Q. 2 What is the most likely pathophysiology?
A) Acetylcholine receptor antibodies
B) Acetylcholinesterase antibodies
C) Acetylcholine deficiency
D) Acetylcholine receptor mutation
E) Acetylcholinesterase mutation

Q. 3 Pyridostigmine was started but unfortunately he re-presented with worsening weakness and inability to chew. What is the next line in treatment?
A) Referral for PEG feeding
B) Start prednisolone
C) Start ciclosporin
D) Transfer to PICU for plasmapheresis
E) Intravenous immunoglobulin 1 g/kg daily for 2 days

Answers

Case 1

Q.1- A, Q.2- B, Q.3- C.

Discussion

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder that affects the motor neurons. It is characterised by degeneration of alpha motor neurons in the spinal cord, resulting in progressive proximal muscle weakness and paralysis.

It was first described in the 1890s by Werdnig and by Hoffmann. Survival motor neuron gene (SMN) was identified in 1995. SMA is the second most common fatal autosomal recessive disorder after cystic fibrosis, with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births, with a carrier frequency of 1/40-1/60.

It is classified into four phenotypes on the basis of age of onset and motor function achieved.

(a) SMA type 1 (Werdnig-Hoffmann disease) is the most severe and common type, which accounts for about 50% of patients diagnosed with SMA. The onset of clinical signs is seen before 6 months of age. The affected individuals never acquire the ability to sit unsupported and, if no intervention is provided, generally do not survive beyond the first 2 years. These children have profound hypotonia and symmetrical flaccid paralysis. The facial muscles are spared. These infants have a typical respiratory pattern in the form of paradoxical breathing due to sparing of diaphragm along with weakened intercostal muscles. The important cause of morbidity and mortality is aspiration pneumonia.
(b) SMA type II is characterised by onset between 7 and 18 months of age. Affected individuals may achieve the ability to sit unsupported or even stand with support, but they do not acquire the ability to walk independently. Joint contractures and kyphoscoliosis are very common which can occur in the first years of life. Children who are able to sit unsupported are usually more prone to respiratory signs and early scoliosis.
(c) SMA type III (Kugelberg-Welander disease) includes clinically heterogeneous patients. Affected children typically reach all major motor milestones and can achieve independent walking. They further develop proximal muscular weakness and some need wheelchair assistance in during their childhood.
(d) SMA type IV has been added to this classification to describe those patients with adult onset (more than 18 years) and a mild course.

Molecular genetics

Two almost identical SMN genes are present on chromosome 5q13-SMN1 and SMN2. About 95% of patients have a homozygous disruption of SMN1 due to deletion or