Electrical inexcitability of nerves and muscles in severe infantile spinal muscular atrophy

Spinal muscular atrophy (SMA) is one of the most common fatal autosomal recessive disorders, characterised by progressive degeneration of anterior horn cells. Before the advent of genetic testing, the diagnosis of SMA was based on clinical, histopathological, and electrophysiological features. In 1992, the International SMA Consortium defined diagnostic criteria of proximal SMA based on clinical findings.[1] In SMA type I (severe; Werdnig-Hoffmann disease), affected persons have onset of symptoms before 6 months of age and are never able to sit without support. Electromyography demonstrates denervation features. In early 1995, the candidate gene, the survival motor neuron (SMN) gene, was identified, making the confirmation of SMA by DNA analysis possible.[2]

With the availability of a genetic test for SMA, many investigators are refining the diagnostic criteria published by the Consortium. Studies involving hundreds of patients with proximal SMA have disclosed a subset of patients who fulfill at least one exclusion criterion defined by the Consortium.[3] We identified an infant with severe SMA who fulfilled two exclusion criteria and also showed inexcitability of all nerves as well as muscles. This report will further delineate the wide range of phenotypes for this particular gene mutation.

A 2945 g male infant was born at term. First fetal movements were noted at 13 weeks of gestation. Chorionic villus sampling at 10 weeks of gestation disclosed normal chromosomes. Decreased fetal movement and polyhydramnios were noted at about 34 weeks of gestation. At delivery, the infant was cyanotic with no respiratory effort and was subsequently intubated. On physical examination, the infant had no spontaneous movements. He opened his eyes with brief fixation but no following. Tongue fasciculations were present. Other cranial nerves seemed intact. Mild flexion contractures of both elbows, knees, and ankles were noted. Tone was flaccid in both upper and lower limbs, and there was no movement response to painful stimulus. Deep tendon reflexes were absent.

Brain MRI disclosed mild diffuse cortical and deep atrophy. His EMG was severely abnormal, with widespread fibrillations and absent voluntary motor units except in the genioglossus, where mildly neurogenic motor units with decreased recruitment were seen. Stimulation of the median, ulnar, tibial, and peroneal nerves with a maximal stimulus resulted in no clinical or electrical response. The biceps brachii and rectus femoris muscles were electrically inexcitable by direct needle stimulation. Median, ulnar, and sural sensory potentials were not obtainable. DNA testing showed a homozygous deletion of exons 7 and 8 in the telomeric SMN gene, confirming the diagnosis of SMA. The infant expired at 3 weeks of age, and the parents declined postmortem examination.

Typical EMG studies in those with SMA show fibrillations and fasciculations at rest and an increased mean duration and amplitude of motor units. Motor nerve conduction velocities may be slowed but are usually normal. Korinthenberg *et al* reported inexcitability of motor nerves in three siblings, each of whom died from SMA before 1 month of age.[4] In addition to a homozygous deletion of exons 7 and 8 of the telomeric SMN gene, all three siblings showed a large deletion in the region that includes all alleles of the multicopy markers Ag1-CA and C212, localised at the 5' end of the two SMN gene copies. It has been postulated that the severity of disease may be correlated to the extent of a deletion involving the SMN gene and the multicopy markers.[3–5] The infant in our report with SMA type I showed electrical inexcitability of motor nerves as well as the characteristic alteration of the SMN gene.

Although it has been known for some time from histological studies that sensory systems are involved in SMA, electrophysiological sensory findings have been previously reported only once.[4] Sensory nerve conduction velocity was tested in an infant with severe SMA and showed no recordable potential, but the infant in our report also exhibited universal absence of sensory potentials. In both cases, DNA analysis disclosed the 5q deletion. It is unclear whether this finding represents a distinct entity or merely the severe end of classic Werdnig-Hoffmann disease. The diagnostic criteria produced by the International SMA Consortium currently lists "abnormal sensory nerve action potentials" as an exclusion criterion.[1] Our finding of absent sensory potentials in a 5q deletion established case of SMA indicates further need for revision of the Consortium criteria.

Studies involving large series of patients with SMA have identified cases of SMA variants.[3] These patients were diagnosed as infantile SMA by the presence of proximal weakness and atrophy, hypotonia, and evidence of neurogenic alterations in EMG and muscle biopsy. In addition, these patients also exhibited one of the exclusion criteria defined by the Consortium—for example, diaphragmatic weakness, involvement of the CNS, or arthrogryposis. Although these patients did not show the typical SMN deletion and were therefore probably not linked to chromosome 5q, they could have had point mutations. The infant in our report showed no respiratory effort after birth, indicating diaphragmatic weakness. He did, however, possess the characteristic SMN gene alterations. This finding suggests that diaphragmatic weakness should be reconsidered as an exclusion criterion by the Consortium.

Review of the literature disclosed no previous reports of electrically inexcitable muscles in SMA. This phenomenon is known to occur in a few other neuromuscular conditions such as periodic paralysis and critical illness polyneuropathy. Fibrillations, as seen in the infant in our report, are commonly seen in acute denervation and are thought to be caused by perturbation of the sarcolemmal membrane, rendering it unstable. One possibility may be that the severe denervation in SMA type I can result in abnormal function of the membrane to make it electrically inexcitable. Further electrophysiological studies at the cellular level are required to delineate this interesting finding.

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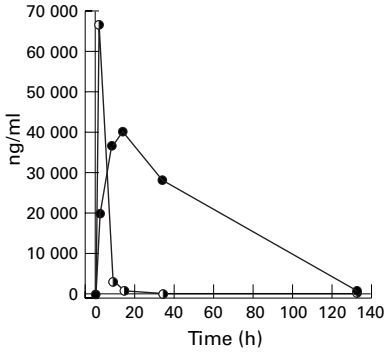
Acute overdosage and intoxication with carbidopa/levodopa can be detected in the subacute stage by measurement of 3-*o*-methyldopa

Although the effects of a chronic overdosage with levodopa are well known, few cases of acute intoxication have been described.[1 2] A particular problem in establishing a diagnosis of levodopa overdosage is the relatively short half life in the circulation of levodopa.[3 4] If there is a delay in bringing an acutely intoxicated patient to hospital, perhaps due to late discovery, the blood concentration of levodopa could already be normal (corresponding to the peak levodopa concentration in Parkinson's disease therapy) after 6–8 hours. Depending on the extent of the overdosage, the time could be even shorter. This report describes the clinical effects and the plasma concentrations of levodopa and specific metabolites over a period of 132.5 hours after ingestion of 30 tablets of carbidopa/levodopa (50 mg/200 mg tablets).

A 76 year old patient had a pre-existing mild akinetic rigid Parkinson's syndrome, which had been treated for the past 1.5 years with 3×1 tablets of carbidopa/levodopa (50 mg/200 mg) a day without a substantial response. The weight of the patient was 74 kg. A known chronic obstructive airway disease was treated with a home oxygen appliance. At about 8.30 pm, the patient had attempted suicide by taking 30 tablets of carbidopa/levodopa. About 9.00 pm he appeared psychically altered, crying without reason, anxious, and depressed. After about 30 minutes he was increasingly inadequate, agitated, and subeuphoric, and was experiencing visual hallucinations; he was restless, tossing and turning, and getting out of bed. He did not represent peak dose dyskinesia or other extrapyramidal clinical features. At 10.00 pm he showed bilaterally maximally dilated pupils. The muscle stretch reflexes were lively, there were no pyramidal tract signs, and he did not show any signs of Parkinson's syndrome or dyskinesia. Arterial hypertonus and sinus tachycardia could be registered.

After an empty box of Striaton (carbidopa/levodopa, 50 mg/200 mg) was found in the patient's flat, 1 g of carbon was given by stomach tube after gastric lavage. Cranial CT was carried out before the diagnosis of intoxication had been made; it showed a pronounced subcortical arteriosclerotic encephalopathy with reduced brain volume. The patient was moved to the medical intensive care unit and observed for 24 hours. The ECG showed a P pulmonale, but no other unusual features. Echocardiography showed normal right and left ventricular function with suspicion of right ventricular hypertro-



Time course of the measured concentrations of levodopa (half filled circles) and 3-o-methyldopa (full circles) after an overdose of levodopa (6000 mg). The peak of 3-OMD appears after a delay, and the concentrationen falls very slowly, corresponding to a half life in plasma of 16.7 hours.

phy. Blood was taken for the measurement of levodopa and metabolites 2.5 hours after ingestion, and again after 9, 14.5, 34, and 132.5 hours. Using high performance liquid chromatography with electrochemical detection, we measured the plasma concentrations of levodopa, 3-*o*-methyldopa, dihydroxyphenylacetic acid, homovanillic acid, noradrenaline, adrenaline, and dopamine. The time course of the concentrations of levodopa and 3-*o*-methyldopa are shown in the figure.

After 24 hours the patient was moved from the intensive care unit to a normal medical ward. At this point no neuropsychiatric signs of levodopa intoxication could be detected. Clinically, the most prominent symtoms of levodopa overdosage are confusion, agitation, sleeplessness, and excessive motor activity. The initial levodopa concentration in our patient was 66 763 ng/ml, the concentrations of DOPAC, homovanillic acid, noradrenaline, adrenaline, and dopamine were raised 2.5 hours after ingestion and rapidly returned to normal. A very noticeable feature of this case was the maximal bilateral mydriasis, with absent light reaction, at the time of the maximal intoxication with a 30-fold increase in plasma levodopa concentration. To our knowledge, this association of a levodopa intoxication with maximally dilated, light unresponsive pupils and without signs of dyskinesia has not previously been reported. It can be assumed that the effect is caused by the peripheral conversion of levodopa into noradrenaline, which stimulates α-adrenergic receptors in the dilatator iridis. There is no indication from animal experiments of a specific activation of dopamine receptors.[5] The arterial hypertonus measured initially can also be attributed to the high systemic concentrations of noradrenaline, and the tachycardia to the raised concentrations of adrenaline and dopamine. As seen in the figure, the only indicator which can show a levodopa intoxication in the subacute stage is the concentration of 3-*o*-methyldopa. The metabolite 3-*o*-methyldopa results from the *o*-methylation of levodopa, which explains the delayed peak of the 3-*o*-methyldopa concentration. The half-life of 3-*o*-methyldopa in plasma was calculated at 16.7 hours in this patient. On the other hand, the plasma half life of levodopa was 111 minutes; this is slightly longer than normal, and can be explained by assuming a rate limited metabolism of levodopa when the substrate concentration for the enzymes metabolising it is raised.

Distribution into muscles rather then metabolism may largely determine the plasma half life of levodopa and explain why this was only slightly altered with overdose. The measured peak concentration of 66 763 ng/ml is about 30 times higher than the peak concentration to be expected after taking one tablet of carbidopa/levodopa (50 mg/200 mg). It is apparent that the 30 tablets did not interfere with absorption or lead to a gastrointestinal paralysis due to the high dose of levodopa; the relation between amount ingested and plasma concentration seems to be linear, at least in this dose range.

We conclude from these findings that in cases of suspected levodopa intoxication some hours previously, it could be important to measure the concentration of 3-*o*-methyldopa, so as not to overlook an overdosage with levodopa, which may be due to a suicide attempt. In addition to the diagnostic uncertainty in relation to the immediate treatment of the patient, this would also have an effect on further psychiatric and psychological therapy.

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The use of olanzapine for movement disorder in Huntington's disease: a first case report

Movement disorder is a prominent feature of Huntington's disease and consists of involuntary and voluntary components as well as associated bradykinesia. Pharmacological treatment is problematic because of the side effects of the drugs used, which may further compromise cognitive functioning and mobility. Patients are often not subjectively aware of their movements but can be considerably disabled by them and carers are often distressed and enquire about treatment options. If drug treatment is considered it is important to achieve the maximum improvement in movements with the minimum of negative side effects. This paper describes the effect of olanzapine on movements when other treatment options had been ineffective or limited by side effects.

Huntington's disease is a hereditary progressive neurodegenerative disorder. It consists of a triad of symptoms comprising motor, psychological, and cognitive abnormalities. The motor component consists of involuntary choreiform movements and increasing difficulties with voluntary movement. The degree of the involuntary movements is variable but in some patients can be very marked. Progression over time of the movement disorder in Huntington's disease can be monitored using the quantitative neurological examination (QNE). This measure has three subscales, an eye movement scale, a motor impairment scale (MIS) quantifying voluntary movement, and a chorea scale measuring involuntary movement.[1 2]

Pharmacological control of the symptoms has been shown to be effective with dopamine antagonists,[3 4] but their use is limited because of the side effects. Clinically the most problematic of these are sedation, cognitive slowing, increased mobility problems, and hypotension. The inability of traditional dopamine antagonists to improve functional capacity, despite ameliorating chorea, is possibly due to suppression of voluntary motor activity.[4 5] Tardive dyskinesia has occasionally been reported in patients with Huntington's disease treated with these drugs.[5 6] The atypical antipsychotic clozapine has been shown to be effective in improving the movement disorder. However, in a double blind randomised trial of clozapine which included patients who were already receiving traditional antipsychotic medication and a group who had not received drug treatments for their movement disorder, chorea was reduced in those who were antipsychotic naive only and the authors concluded that clozapine was of little additional benefit in Huntington's disease.[7] Olanzapine is a new atypical antipsychotic drug. It is a thienodibenzodiazepine structurally very similar to clozapine. Unlike clozapine it is not associated with the potentially serious side effect of agranulocytosis and therefore frequent blood monitoring is not necessary.

This report describes the progress of a man who has Huntington's disease. He developed a marked movement disorder and was unable to tolerate both sulpiride and risperidone but had symptomatic improvement when treated with olanzapine.

He is a man in his early 50s who had a confirmatory genetic test for Huntington's disease in 1994, after the development of clinically obvious motor symptoms. It is likely that the onset of symptoms had occurred a few years previously as he had experienced difficulties in concentration and attention at work, attributed at the time to stress, leading to the loss of employment. In addition his family, watching family videos of a few years earlier, thought that there was evidence of early signs of his movement disorder. However there was no known family history of Huntington's disease which might have led to an earlier diagnosis. By May 1995 his involuntary movements were becoming more noticeable, although control of voluntary movement was good. A trial of sulpiride commencing at 200 mg twice daily and increasing over 1 week to 800 mg daily was undertaken with a subsequent decrease in the frequency and extent of involuntary movement recorded in case notes; unfortunately the QNE was not repeated at this time. However, the patient experienced a subjective slowing of his cognitive processes, concurrently became depressed, and decided to stop the treatment within 3 weeks. Paroxetine, a selective serotonin reuptake inhibitor antidepressant, was started at a dose of 20 mg a day, which led to an improvement in his low mood. His involuntary movements continued to cause difficulties in his daily living. He was unable to sit comfortably in a chair and when out he felt that he was disturbing others by knocking into them. He agreed to a trial of