Pathophysiology of the intermediate syndrome of organophosphorus poisoning

We report a patient with the intermediate syndrome with results of repetitive nerve stimulation studies and single fibre EMG. A hypothesis for the pathophysiology of the intermediate syndrome is proposed.

A 28 year old previously healthy Asian woman drank a bottle of organophosphate (about 60 ml). She was admitted swiftly to hospital and treated with gastric lavage and intravenous atropine and a single dose of pralidoxime. After three to four days she developed respiratory weakness and was unable to lift her head. On the fifth day her vital capacity fell. Her facial muscles were weak, as was shoulder abduction and hip flexion. The distal muscles were normal. She had normal reflexes and no sensory deficit. She was intubated, respirated, and atropine was continued.

Her muscle strength slowly improved and she was weaned from the respirator on the 15th day she was neurologically normal. Neurophysiological studies were carried out on the 7th, 14th, and 18th days. She recovered completely after three weeks. Results from motor and sensory weakness and was able to lift her head. On the fifth day her vital capacity fell. Her facial muscles were weak, as was shoulder abduction and hip flexion. The distal muscles were normal. She had normal reflexes and no sensory deficit. She was intubated, respirated, and atropine was continued.

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No decremental responses were seen at rates up to 50%; nor was a decrement present after one minute of exercise or after 10 seconds of repetitive stimulation at 20s or 50%. Incremental responses were not seen. Single fibre EMG from the clinically normal extensor digitorum communis showed two single fibre pairs with borderline jitter values; the mean consecutive difference (MCD) was 59 and 60 ms, respectively. Frontalis muscle was examined on day 7 and showed increased jitter with blocking. Of 17 fibre pairs, 12 had increased jitter and seven of these had greater than 10% blocking (figure). As expected, blocking was only seen in pairs with a considerably raised MCD.

The intermediate syndrome follows the acute cholinergic crisis of organophosphorus poisoning and is seen in up to 20%–50% of cases depending on the severity of poisoning and duration, and on the type of organophosphorus compound.1 It differs from myasthenia gravis in that it is a constant rather than progressive weakness, responds adversely to neostigmine, and recovers within 18 days. There are no associated autoimmune phenomena. Dependent responses to repetitive nerve stimulation have been seen sometimes but usually it has been the clinically unaffected peripheral muscles that were studied.

We propose that down regulation of acetylcholine receptors (AChRs) could explain the syndrome and neurophysiological findings. These receptors have a half life of 10 days before undergoing endocytosis and proteolysis within nerve fibres.2 Regulation of the number of AChRs and

patients with relapsing-remitting multiple sclerosis, not in the one with chronic-progressive multiple sclerosis. Il-1β was not detectable in serum (n = 118 samples) or CSF (n = 33 samples). Il-1β could be detected in all serum samples but not in CSF. Hence serum Il-1β concentrations were subject to further analysis. The median serum Il-1β concentrations varied individually (range 45–422 pg/ml), but were all below the detection limit (< 15 pg/ml). Three of the patients with the highest total number (64) of Gd enhancing lesions (patient 1), an increase or decrease of MRI activity was followed by an increase or decrease of Il-1β concentrations by three to four weeks (one time point, P < 0.05 in sign test, figure). Individually defined extreme Il-1β concentrations were only seen in patients with relapsing-remitting multiple sclerosis. There were four such extreme concentrations in four different patients. Two of those coincided with relative maxima of MRI activity, and one with a clinical (spinal) relapse.

Smaller time courses of Il-1β concentrations Il-1β were not specific for multiple sclerosis activity, as they were also found in the group of patients with chronic-progressive multiple sclerosis and a high MRI activity in the observation period. This is probably due to the fact that Il-1 and Il-1β are involved in a wide range of inflammatory activities.7 The longitudinal design including monthly visits proved to be particularly effective in detecting individual extreme Il-1β peaks. Because of the few patients, a significant association could be shown in only one patient. In her, the very high disease load (demonstrated by MRI activity) probably allowed us to detect this association. We could not detect Il-1β in CSF, or Il-1β in CSF or serum, probably because the concentrations were below the detection limit of our ELISA assays. Because the biologically active concentration of Il-1β is at least one magnitude higher than that of Il-1,8 Il-1β may be more easily detectable than Il-1.

In conclusion, we found that fluctuations of Il-1β may be associated with multiple sclerosis activity. The role of Il-1β in multiple sclerosis therefore warrants further study.

Raymond Voltz, Mathias Hartmann, Caroline Spuler, Angelika Scheller, Norbert Mai, Reinhard Höfheld

Department of Neurology, Klinikum Großhadern, University of Munich, Munich, Germany

Tarek Youssry
Department of Neurology, Klinikum Großhadern, University of Munich

Correspondence to: Dr Voltz, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021, USA


mechanisms for up regulation and down regulation are not fully understood but lack of activity—for example, after denervation or nerve conduction block—results in up regulation. Down regulation is seen in myasthenia gravis, in which the receptors are destroyed by autoimmune mechanisms. There is experimental evidence of down regulation of AChRs in the presence of agonists.1

Down regulation of AChRs in the presence of AChE inhibition would be expected to cause a different syndrome from myasthenia gravis. In myasthenia gravis the progressive weakness is explained by the smaller amounts of ACh released at the neuromuscular junction with each successive nerve impulse. The reduced number of ACh molecules are less likely to activate the few remaining AChRs before they are enzymatically destroyed. In the intermediate syndrome, however, any liberated ACh is likely to have time to activate one or more receptors once or even several times before it diffuses away. Receptor activation, however, fails to produce muscle contraction because there are insufficient simultaneously activated receptors. Even exposure to small amounts of organophosphorus can cause transient increase in jitter.1

If the half life of AChR is 10 days, why should intermediate syndrome appear so rapidly 24–96 hours after poisoning? A reason may be that heavily activated receptors become desensitized, rendering them more readily endocytosed. The process may be related to the increased postjunctional non-contractile Ca2+.1 Recovery from intermediate syndrome in 5–18 days is explicable in terms of the AChR production.

With few AChR receptors an increase in single fibre jitters with blocking would be expected as it is more difficult to depolarise the fibre to firing threshold. However, even the reduced amounts of ACh released late in tetanic trains would be enough to activate all the receptors available. Repetitive stimulation would be expected to show neither increment nor decrement.

Although this sequence of events cannot be confirmed by clinical studies, supportive evidence could be obtained by estimating AChR numbers from end plate biopsies and more detailed single fibre EMG studies.

EM SEDGWICK
Clinical Neurological Sciences, Faculty of Medicine.
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E M Sedgwick and N Senanayake

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