stimuli as she performed normally on a routine cancellation task and performed well on a version of the task in which she had to cancel objects after seeing their picture. The most parsimonious explanation for the patient's performance is that she had more difficulty matching the semantic description of a target and its visual appearance when that object was on the right. Given the wide variety of phenomena captured by the term neglect it would seem permissible to refer to the patient's performance as "semantic neglect."

Although clinically neglect is most often seen in its spatial form, neglect behaviour is not monolithic. Either attentional or intentional deficits may pertain in different cases,[3] and patients may show neglect on line bisection tasks but not cancellation tasks or vice versa.[4]

Neglect may also be relatively modality specific. Baxter and Warrington[5] reported a patient who made misspellings on the left side of words, whether spelled forwards or backwards. This patient did not show other overt features of visuospatial neglect. Leicester *et al*[6] used a paradigm in which patients made their response by selecting from a 3×3 array of targets. Stimuli (letters of the alphabet) were presented in auditory, visual, or tactile modes. Some of the patients of Leicester *et al*[6] showed neglect when presented with the letters in only one or another mode; even when the targets were identical.

Neglect dyslexia is an additional example of a modality specific neglect that may not be explained by defective spatial attention. In neglect dyslexia patients may omit, but more commonly substitute or alter, letters when reading single words. Thus patients may read "bear" or "ear" when shown the word "hear." Whereas some cases of neglect dyslexia may be mediated by spatial mechanisms, in many cases there is no definite evidence of spatial neglect.[7] Further, neglect dyslexia has been shown to be disassociable from spatial hemineglect.[8]

That the defect in neglect dyslexia may be related to neural systems subserving language can be inferred from patient response characteristics. Response accuracy in neglect dyslexia may be greater for real words than for non-words,[9] indicating top down lexical influences on severity of neglect dyslexia. Neglect dyslexia is relatively insensitive to word length, suggesting that the abnormality is not at the level of the processing of the visual stimulus but rather at the level of handling the "word" form.[7]

In summary, the patient reported was more likely to neglect a target when it was on the right and the stimulus was presented verbally. Given this combination it is suggested that the patient had "semantic neglect." This finding is consistent with the evidence that neglect is not monolithic and may be modality restricted. That neglect behaviour often seems due to a schism along a spatial-language divide is consistent with the hypothesis that as the neural networks of the left hemisphere subserving language arose they coopted neural structures of the left hemisphere utilised for directed spatial attention.[10]

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Prolonged neurological sequelae after combination treatment with lithium and antipsychotic drugs

A 24 year old woman, previously diagnosed as having a manic depressive psychosis, had episodes of mania in 1990 and 1992, during which she had been treated with lithium, (up to 1800 mg/day) with good recovery.

Four weeks before current admission to hospital, she had again become restless and sleepless and talked excessively. The same psychiatrist was consulted. She was started on lithium at 450 mg/day. The symptoms persisted and the dose of lithium was increased to 900 mg/day and then 1050 mg/day and 20 mg/day of haloperidol was added on day 7. On day 10 she developed mild tremors of the hands and diarrhoea but the psychiatric symptoms persisted. On day 16, she was switched over to a sustained release preparation of lithium at 1000 mg/day, Haloperidol was increased to 30 mg and chlorpromazine (100 mg/day) was added. The diarrhoea and tremors increased and she now developed lethargy, unsteadiness, and vomiting. All medications were stopped on day 22. Serum lithium concentrations were not measured. On day 24 she was rigid with extensor posturing and eyes deviated upwards. She was febrile, incontinent, and seemed awake, but did not respond to command. She was transferred to our hospital on day 28. We found the patient afebrile, with normal pulse and blood pressure. She was conscious but stared blankly, was unresponsive to commands, and winced with painful stimuli but did not move her limbs. She had spontaneous vertical nystagmus and occasional opsoclonus. Optic fundi were normal. All limbs were rigid. Deep tendon reflexes were normal and plantar responses were flexor. Serum creatine phosphokinase was raised on admission (1002 IU, normal range 175–200 IU) but had returned to normal by day 4. There was persistent leukocytosis. Examination of CSF and metabolic variables measured were normal. Serum lithium concentration on admission, six days after stopping lithium, was 0·8 ng/dl (normal 0·5–1·5 ng/dl.) Brain CT showed minimal bilateral basal ganglia calcification; Brain MRI was normal. An EEG showed mild diffuse background slowing, without any focal features. The patient remained afebrile. Over the next few days limb stiffness became less but she still had a vacant immobile face and did not respond to commands or show any voluntary activity. Six weeks later the nystagmus had disappeared but she remained immobile. She could now comprehend and communicate yes and no answers with eye movements and blinks. At 10 weeks, voluntary movements returned to the face. Neck and upper limb power returned next. She had finger-nose ataxia, and her speech was slurred and explosive. Mild rigidity persisted and a fine resting tremor appeared in the limbs. Five months later, the patient continued to have pronounced dysarthria and ataxia with brisk deep tendon reflexes.

Neuroleptic malignant syndrome was excluded by the absence of fever, dysautonomia, or raised creatine phosphokinase. The normal CSF and MRI ruled out encephalitis or demyelinating disease. We therefore attributed the clinical features in our patient to lithium neurotoxicity.

Lithium neurotoxicity is usually seen during long term treatment, although acute neurotoxicity has occasionally been encountered. The manifestations are usually reversible. Most patients with lithium toxicity have high serum lithium but some experience neurotoxicity at therapeutic concentrations.[1] This is because lithium concentration in nervous tissues may be several times greater than the serum concentration. Thus intracellular (red blood cells) lithium concentrations may be a more accurate guide to monitor toxicity. Our patient had developed toxic symptoms after a short course of lithium and had normal serum lithium concentrations on admission to our hospital; concentrations may have been higher earlier. Measures to increase lithium excretion are useful when serum concentrations are high. We did not attempt these as their role in neurotoxicity when serum lithium concentrations are normal is not clear.

Extrapyramidal features, which were prominent in our patient, are rare in lithium toxicity. Moreover, toxic manifestations are usually transient whereas our patient was incapacitated six months after stopping lithium. Cohen *et al* have described four patients who were receiving lithium and haloperidol when they developed extrapyramidal features.[2] As in our patient, these persisted for months or years. The authors warned about the potential permanent sequelae on this drug combination. Donaldson *et al* described 13 patients with chronic sequelae, two of whom had extrapyramidal disorders.[4] Both had received lithium and haloperidol. Our patient had received lithium on two previous occasions, at a higher dose, without complications. The only difference this time was the addition of antipsychotic drugs. It is likely that haloperidol and other dopamine receptor blocking drugs may increase sensitivity to the lithium ion in some patients, and result in neurotoxicity. Curiously, our patient as well as the six previously described were all females.

Our patient's CT disclosed minimal basal ganglia calcification, which was asymptomatic. Abnormal brain tissue may have a reduced capacity to excrete lithium, leading

to islands of neurotoxicity.[4] A contribution from the otherwise insignificant basal ganglia calcification to the extrapyramidal features in our patient is doubtful.

The highest concentrations of lithium in the CNS are found in the white matter of the pons.[4] At one stage, our patient was totally immobile except for eyeblinks and eye movements, with which she could communicate. A normal MRI ruled out central pontine myelinolysis. Could this state, therefore, be attributed to the high concentration of lithium in the pons?

In conclusion, lithium neurotoxicity usually develops after chronic treatment. Permanent sequelae are rare but the occasional occurrence of acute and persistent neurological symptoms warrants a note of caution, especially when lithium is used in combination with antipsychotic drugs.[5] Lithium, preferably intracellular (red blood cells) should be carefully monitored to avoid neurotoxicity. Rarely, neurological sequelae may develop even at therapeutic serum concentrations. Therefore, the need for keen clinical observation, in addition to routine drug monitoring, especially during combination treatment with antipsychotics, cannot be overemphasised.

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Pure autonomic failure with motor neuron disease: report of a clinical study and postmortem examination of a patient

From clinical and pathological viewpoints, primary chronic autonomic failure is divided into three types: pure autonomic failure without other neurological conditions, autonomic failure with multiple system atrophy, and autonomic failure with Parkinson's disease.[1] In pure autonomic failure, the main pathological findings were neuronal loss in the intermediolateral columns of the spinal cord and the occurrence of eosinophilic bodies in the sympathetic ganglia. Furthermore, Lewy bodies in the substantia nigra or locus coeruleus were also described.[2 3] Because the necropsied cases of pure autonomic failure always showed Lewy bodies in the brainstem, it has been considered as an extreme variant of autonomic failure with Parkinson's disease.[1] Our patient was a man with pure autonomic failure whose prominent symptom was orthostatic hypotension, and who showed the neuropathological changes reported in pure autonomic failure as well as those in a familial form of motor neuron disease.

A 78 year old man had claimed dizziness on standing for the past five years. At the age of 76, he had noted frank syncope which gradually increased in frequency. No other symptoms had been experienced until the last year, when he was admitted to our hospital. He had had chronic bronchitis for the past 10 years. There was no family history suggesting neuromuscular diseases. On admission, physical examination disclosed severe orthostatic hypotension and diffuse mild weakness of the limb muscles. Muscle tone and deep tendon reflexes were normal. Pathological reflexes, muscle atrophy, fasciculation, cerebellar ataxia, and sensory disturbance were not seen.

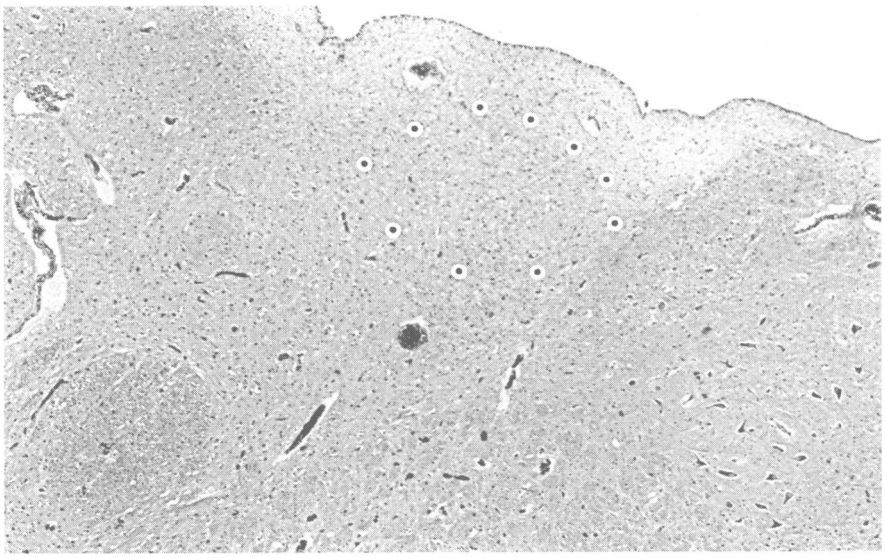

Figure 1 Dorsal vagal nucleus (dotted outlines) showing severe neuronal loss (haematoxylin-eosin × 120).

Laboratory studies of blood, urine, and CSF were within normal limits. A chest radiograph showed mild reticular changes in the lower fields of the lungs. Cranial CT, MRI, and ECG showed no abnormal findings. Needle EMG and nerve conduction studies were not performed. A blood pressure of 106/30 mm Hg in the supine position decreased to 50/30 mm Hg on head up tilt, with no change in the heart rate (58 bpm). There was no postural change in serum noradrenaline concentration (0·03 ng/ml (controls: 0·05–0·40 ng/ml)), although plasma renin activity and serum arginine vasopressin were appropriately increased. The cold pressor test caused a decrease in blood pressure, from 104/54 to 90/50 mm Hg. An exaggerated increase in blood pressure (from 100/40 to 186/100 mm Hg) was obtained after treatment with intravenous noradrenaline. The coefficient of variation of the mean R-R interval of the ECG was reduced to 0·39% (controls > 1·14%). Intravenous infusion of atropine induced no change in heart rate. The phase IV overshoot of blood pressure after a Valsalva manoeuvre was absent. The pupillary responses to the instillations of both 5% tyramine and 1·25% noradrenaline were normal. The Schirmer test showed decreased lacrimation. Volume of residual urine was 10 ml and cystometry was normal. The patient died of subacute interstitial pneumonia eight months after admission.

His brain weighed 1020 g. Macroscopic findings were not remarkable. Paraffin sections were stained with haematoxylin-eosin, cresyl violet/Luxol fast blue, and silver impregnation (Bodian stain, Gallyas stain). Immunohistochemical staining with the avidin-biotin peroxidase procedure for identification of ubiquitin and phosphorylated high molecular weight neurofilaments was carried out. Multiple sections from various cortical areas including the precentral gyrus were unremarkable. No neuronal inclusions could be identified. Neuritic plaques were absent. Neurofibrillary tangles were noted only in the hippocampus. The striatum, globus pallidus, thalamus, subthalamic nucleus, and hypothalamic nucleus appeared normal. The cerebral white matter was unremarkable. No glial cytoplasmic inclusions were noticed. The substantia nigra and locus coeruleus were examined at two and four different levels, respectively. Several sections from each level were stained with haematoxylin-eosin and immunohistologically with antibodies against ubiquitin and neither neuronal loss nor Lewy bodies were detected. The oculomotor and Edinger-Westphal nuclei showed normal appearances. Mild neuronal loss and gliosis had occurred in the facial and hypoglossal nuclei. In both nuclei, chromatolytic neurons and intracytoplasmic Lewy body-like hyaline inclusions were occasionally noted. Almost total neuronal loss was found in the dorsal motor nuclei of the vagal nerve (fig 1). The accessory cuneate nuclei showed mild neuronal loss. The reticular formation in the medulla exhibited mild astrogliosis as well as a few hyaline inclusions. The red nuclei, raphe nuclei, pontine nuclei, inferior olivary nuclei, and pyramids were not affected. In the cerebellum, Purkinje cells were slightly decreased in number, and the dentate nucleus showed a mild degree of grumose degeneration. There was no noticeable myelin pallor of the cerebellar white matter. In the spinal cord, there was severe loss of sympathetic neurons of the intermediolateral columns. This was accompanied by moderate loss of anterior horn motor neurons throughout the thoracic and lumbar cord. Clarke's columns also showed neuronal loss (fig 2A). In the anterior horns, chromatolytic neurons, spheroids, intraneuronal conglomerates, and hyaline inclusions were occasionally encountered. Swollen cord-like axons were seen in the intramedullary portion of the spinal anterior root. Astrogliosis and a few hyaline inclusions were also noted in the intermediate zone of the spinal cord. No pathological findings were recognised in Onuf's nucleus.

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Notes