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- 1 Batocchi AP, Evoli A, Servidei S, Palmisani MT, Apollonio F, Tonali P. Myasthenia gravis during interferon alfa therapy. *Neurology* 1995;45:382–3.
- 2 Riedel RR, Schmitt A, Hartmann A. Ocular pseudo-myasthenic reaction induced by interferon in an AIDS patient. *Klin Wochenschr* 1991;69:930–1.
- 3 Fritze D, Herrman JRC, Naeim F, Smith GS, Zeller E, Walford RL. The biological significance of HL-A antigen markers in myasthenia gravis. *Ann NY Acad Sci* 1976;274:116–29.

Respiratory chain complex I deficiency in an infant with infantile spasms

Infantile spasms are a common epileptic disorder of infants and may be caused by a great variety of brain diseases of metabolic, developmental, chromosomal, perinatal anoxic, and postnatal origin. The number of metabolic disorders associated with infantile spasms is restricted to hyperammonaemic syndromes, phenylketonuria, non-ketotic hyperglycaemia, and pyridoxine dependency.¹ We report an infant with a complex I deficiency of the respiratory chain whose presenting and most conspicuous symptom was infantile spasms. On reviewing the literature the association of these two conditions seems to be extremely rare.

A 7 month old male infant whose prenatal, neonatal, and postnatal history was irrelevant, began to have episodes of spasms several times daily. Developmental milestones were within the normal range. Examination showed mild hypotonia but was otherwise normal. Frequent typical flexor spasms on awakening and in the first stage of sleep were seen. An EEG showed diffuse continuous abnormalities compatible with hypsarrhythmia. The patient was treated with ACTH for six weeks. Both the spasms and the hypsarrhythmia disappeared after the first week of treatment and did not recur. Brain CT was normal. Several blood lactate determinations disclosed a consistent hyperlactacidaemia (60–80 mg/dl) together with normal blood pyruvate. The 24 hour urinary excretion of succinate, fumarate, glutarate, α -ketoglutarate, malate, and lactate was greatly increased. The activities of pyruvate dehydrogenase complex, pyruvate carboxylase, and Krebs' cycle enzymes in fibroblasts were within normal limits. The activities of the respiratory chain complexes in muscle mitochondria (corrected for the activity of citrate synthase) were within the normal range, except for NADH-cytochrome C reductase, which was very reduced. This finding was compatible with complex I deficiency. The infant was given oral coenzyme Q₂, carnitine, riboflavin, and succinate for the next three years. Lactate concentrations have remained mildly increased (40–50 mg/dl), but he has not had further seizures. At four years of age he showed a mild muscle wasting of proximal distribution, and

developmental dysphasia. A muscle biopsy at this age disclosed no definite pathological abnormalities; respiratory chain metabolism in muscle yielded similar results to the previous study.

Seizures, typically partial or myoclonic, are a recognised feature in patients with certain mitochondrial disorders.² However, we are only aware of two previous reports of the association of infantile spasms with a presumed mitochondrial disease. Kamoshita *et al* were the first to describe the appearance of infantile spasms in an infant with pathologically established subacute necrotising encephalomyelitis.³ This disease may be associated with errors of metabolism affecting the respiratory chain or other pathways, but the authors do not provide any biochemical study to suggest a specific metabolic disorder. On the other hand Mäkelä-Bengs *et al* have recently described a mitochondrial DNA 8993 T > G point mutation in several members of a family, two of which had infantile spasms as the presenting symptom and mental retardation thereafter.⁴ Our case adds an uncommon disease as the cause of infantile spasms. Furthermore, we are not aware of any previous report on the association of infantile spasms and a respiratory chain deficiency. This does not necessarily mean that this association is exceptional as the biochemical disorder may have been underdiagnosed. The case reported also shows a rare phenotype for complex I deficiency, but the clinical range of mitochondrial diseases is expanding.² Despite the few cases reported infantile spasms should be considered as one of the forms of presentation of mitochondrial diseases. It also seems advisable to suspect a respiratory chain disorder in infants with the so-called cryptogenic West syndrome.

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- 1 Ogier H, Aicardi J. Metabolic diseases. In: *Diseases of the nervous system in childhood. Clinics in developmental medicine No 115/118*. London: MacKeith Press, 1992:457–60.
- 2 De Vivo DC. The expanding clinical spectrum of mitochondrial diseases. *Brain Dev* 1993;15:1–22.
- 3 Kamoshita S, Mizutani I, Fukuyama Y. Leigh's subacute necrotizing encephalomyelopathy in a child with infantile spasms and hypsarrhythmia. *Dev Med Child Neurol* 1970;12:430–5.
- 4 Mäkelä-Bengs P, Suomalainen A, Majander A, Rapola J, Kalimo H, Nuutila A, Pihko H. Infantile spasms as presenting symptom of mitochondrial DNA 8993 T > G point mutation. *Pediatr Neurol* 1994;11:85.

Semantic neglect?

An aphasic woman with a left posterior hemisphere stroke showed a decreased ability to cancel right sided stimuli when the cancellation was based on matching a picture with a verbal name and description. She showed normal performance on traditional cancellation tasks and cancelling pictures when the object was shown to her visually.

This 49 year old right handed woman was admitted for "decreased speech." For one day she had spoken only in short, automatic

phrases. Commands were obeyed inconsistently, she did not repeat, and her comprehension was poor. She could not read. The Western aphasia battery¹ given 12 days after her ictus, showed an aphasia quotient of 22.8, with the pattern of Wernicke's aphasia. The remainder of the general neurological examination was normal.

A remote right posterior parietal infarction and an acute left posterior temporal-parietal infarction seen on MRI was thought to be secondary to an autoimmune hypercoagulable state. Routine investigations were negative and the patient had a prestroke history of an autoimmune haemolytic anaemia, myasthenia gravis, and lupus anticoagulant.

The patient only identified named pictures on her left but was able to cancel objects well on the right and left sides in a routine cancellation task. To test the impression that the patient was neglecting semantic material on her right a series of cancellation tasks were given.

At the first examination (one week after the stroke) the patient was given two varieties of cancellation task: a routine version and a semantic version. The first version was similar to the standard method developed for assessing neglect in aphasic patients.² For the semantic version the patient was asked to cross out specific objects by name and description (for example—Where is the pencil? The item that you would use to write on a piece of paper?).

On the routine cancellation task the patient cancelled a total of 42 of 45 right sided targets and 42 of 45 left sided targets. There was no difference when the paper was placed to the left or right. Pooling all the semantic task trials 56 of 80 left sided items and 37 of 80 right sided items were detected ($P = 0.004$, Yates' correction $\chi^2 = 8.32$, $df = 1$). Placing the entire page to the patient's left or right did not change performance. Of the 30 semantic items used 12 were detected more often when they were on the left, three when they were on the right, and 15 were detected equally regardless of side ($P = 0.02$, $\chi^2 = 7.8$, $df = 2$).

Was the patient's performance due to different attentional demands for the two versions of the task? In the traditional cancellation task the patient was simply finding any object on the page. In the second version of the task she had to find a specific individual object. To evaluate if this mechanism explained the patient's performance, the patient was retested 12 weeks after the stroke. The mechanics of testing were similar to the first examination.

In the routine task the patient was asked to cancel all the objects on a page regardless of identity or location. In the pictorial version she was shown a picture of the object she was to cancel. In the semantic version of the task the patient was told which object to cancel.

The patient's performance had improved in the three months since her stroke. She was flawless on the routine cancellation task. She showed a disproportionate number of errors in the identification of objects on the right side of the page when they were named versus when they were presented visually or when they were cancelled regardless of their identity ($\chi^2 = 14.9$, $df = 5$, $P = 0.01$). When the patient was asked to cancel objects by name and description there was a significantly greater risk of omission if the object to be cancelled was located to the patient's right. Her performance was not due to an inability to see or attend to the

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 Warrington⁵ 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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- 1 Kertesz A, Poole E. The aphasia quotient: the taxonomic approach to measurement of aphasic disability. *Can J Neurol Sci* 1974;1: 7-16.
- 2 Albert M. A simple test of neglect. *Neurology* 1973;23:658-64.
- 3 Tegnér R, Levander M. Through a looking glass. A new technique to demonstrate directional hypokinesia in unilateral neglect. *Brain* 1991;114:1943-51.
- 4 Binder J, Marshall R, Lazar R, Benjamin F, Mohr JP. Distinct syndromes of hemineglect. *Arch Neurol* 1992;49:1187-94.
- 5 Baxter DM, Warrington EK. Neglect dysgraphia. *J Neurol Neurosurg Psychiatry* 1983; 46:1073-8.
- 6 Leicester J, Sidman M, Stoddard LT, Mohr JP. Some determinants of visual neglect. *J Neurol Neurosurg Psychiatry* 1969;32:580-7.
- 7 Warrington EK. Right neglect dyslexia: a single case study. *Cognitive Neuropsychology* 1991;8: 193-212.
- 8 Costello ADL, Warrington EK. The dissociation of visuospatial neglect and neglect dyslexia. *J Neurol Neurosurg Psychiatry* 1987; 50:1110-6.
- 9 Chatterjee A. Crossover, completion and confabulation in unilateral spatial neglect. *Brain* 1995;118:455-65.
- 10 Anderson B. An inside-out theory of attention. *Med Hypotheses* 1992;39:295-301.

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 con-

centration 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