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Respiratory chain complex I deficiency in an infant with infantile spasms

Infantile spasms are a common epileptic disorder of infancy and can 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 a few inborn errors of metabolism, and it is usually easy to make a correct diagnosis. However, we are not only aware of two previous reports of the association of infantile spasms with a presumed mitochondrial disease. Kamonshita et al have been the first to describe the appearance of infantile spasms in patients with pathologically established subacute necrotizing encephalomyelitis.1 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-Bengt et al have recently described a mitochondrial DNA 8993 T \rightarrow G point mutation in several members of a family, two of which had infantile spasms as the presenting symptom and mental retardation thereafter.2 We can thus add 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 mitochondrial chain deficiency. This does not necessarily mean that this association is exceptional as the biochemical errors have not been understood. The case reported also shows a rare phenotype for complex I deficiency, but the clinical and morphologic features of mitochondrial diseases are expanding.3 Despite the few cases reported infantile spasms should be considered as one of the forms of presenta- tion 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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Semenic 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. The results might have been caused by 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 asked "What is the Western aphasia battery?" 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 evaluation of any other patient not negative and the patient had a pre-stroke 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 vari- ations of cancellation task: a routine version and a semantic version. The task 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 pen- cil? 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 56 of 80 right sided items were cancelled (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 intentional 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 rested 12 weeks after the stroke. The mechanics of testing were similar.

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 had to cancel. In the second 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 more focused on the routine of the 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 rou-
tine cancellation task and performed well on a
version of the task in which CT showed no
trend to cancel objects after seeing their picture. The
most parsimonious explanation for the pa-
tient’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
aphasic 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 inten-
tional deficits may persist in different
forms, and patients may show neglect on line bisec-
tion tasks but not cancellation tasks or vice
versa.4

Neglect may also be relatively modality
specific. Barresi and Warrington reported
a patient who made misspellings on the left
side of words, whether spelled forwards or
backwards. This patient did not show other
ovr features of visuospatial neglect. Leclerc
et al5 reported 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 modality. Some of the patients of Leclerc et al5 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 patient with a modality specific neglect that may not be
explained by defective spatial attention. In
genlex neglect patients may omit, but
more commonly substitute or alter, letters
when reading single words. Thus patients may
write “bear” for “year,” which would be called
word “hear.” Whereas some cases of neglect
dyslexia may be mediated by spatial mecha-
nisms, in many cases there is no definite
evidence of spatial neglect.7 Further, neglect
dyslexia has been shown to be dissociable
from spatial hemneglect.8

That the defect in neglect dyslexia may be related to neural systems subserving lan-
guage can be seen from patient reports and 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 stimuli but rather at the level of han-
dling the “word” form.

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 sug-
gested 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 to 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,
(upto 1800 mg/day) with good recovery.

Four weeks before current admission to hospital, she had again become restless and
eventually 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 after several weeks. Haloperidol was added on day 7. On day 10 she developed
tremors of the hands and diarrhoea but the
psychiatic symptoms persisted. On day 16, she was switched over to a sustained
release preparation of haloperidol (2.5
mg/day) and chlorpromazine (100 mg/day) was
added. The diarrhoea and tremors increased
and she now developed lethargy, unstead-
iness, and vomiting. All medications were
stopped on day 22. Serum lithium concen-
trations were not measured. On day 24 she
was rigid with extensor posturing and eyes
deviated upwards. She was febrile, inconti-
inent, and seemed awake, but did not
respond to command. She was transferred
to our hospital on day 28. We found the
patient afibrile, with normal pulse and
blood pressure. She was conscious but
stared blankly, was unresponsive to com-
mands, and winced with painful stimuli but
did not move her limbs. She had sponta-
neous vertical nystagmus and occasional
oposclonus. 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 (Creatine kinase value was 175–200
IU) but had returned to normal by day 4.

There was persistent leukocytosis. Examina-
tion of CSF and metabolic variables measured were normal. Serum lithium con-
centration on admission, six days after stop-
ping lithium, was 0.8 ng/dl (normal 0.5–1.5
ng/dl). Brain CT showed changes consistent
with focal ganglioneuritis, with mild peri-
roland ganglia calcification; Brain MRI was
normal. An EEG showed mild diffuse back-
ground slowing, without any focal features.

The patient remained afebrile. The next
days limb stiffness became less but she
still had a vacant immobile face and did not
respond to commands or show any volun-
tary activity. Six weeks later the nystagmus
had disappeared but the other features
persisted. She could now comprehend and
communicate yes and no answers with eye
movements and blinks. At 10 weeks, volun-
tary 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 con-
tinued to have pronounced dysarthria
and ataxia with brisk deep tendon reflexes.

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

Lithium neurotoxicity is usually seen dur-
ing long term treatment, although acute
neurotoxicity has occasionally been encoun-
tered. The manifestations are usually
reversible. Most patients with lithium tox-
icity have high serum lithium but some
experience neurotoxicity at therapeutic
concentrations.1 This is because lithium concen-
tration in nervous tissues may be several
times lower 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 concen-
trations are high. We are able to monitor
their role in neurotoxicity when serum
lithium concentrations are normal is not
clear.

Extrapyramidal features, which were
prevalent 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 extrapy-
ramidal 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 extra-
pyramidal syndromes.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 haloper-
idol and other dopamine receptor blocking
drugs may increase sensitivity to the lithium
ion in some patients, and result in neuroto-
icity. Currently 4 of the 6 previously
described were all females.

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

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Semantic neglect?

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