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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 Q₁₀, 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 Mäkela-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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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