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CASE REPORT

Disappearance of epilepsy after resection of catecholamine secreting extra-adrenal paragangliomas: a case report

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ABSTRACT

Epileptic seizures have been associated with increased catecholamine levels, however, direct proof is lacking. We report a case with catecholamine secreting extra-adrenal paragangliomas and a continuous state of epilepsy not responding to therapy. The epileptic seizures resolved after resection of the paragangliomas and normalization of catecholamine excretion.

KEYWORDS

Paraganglioma, epilepsy, noradrenaline

INTRODUCTION

Epilepsy is a disease with a broad array of causes.[1] The association of seizures and catecholamine-producing paraganglioma is rare, mainly described in paediatric cases and few adult cases.[2-5]

We report a patient with catecholamine-secreting extra-adrenal paragangliomas and a continuous state of epilepsy, not responding to therapy. The epileptic seizures resolved after resection of the paragangliomas and normalisation of catecholamine excretion. Hypertensive encephalopathy was not considered to play a causative role as blood pressure levels were well measured and overall in the normal range. The patient was able to discontinue his anticonvulsant therapy. Epileptic seizures and paraganglioma have been associated before, but this is the first case report showing a direct association with increased catecholamine levels.

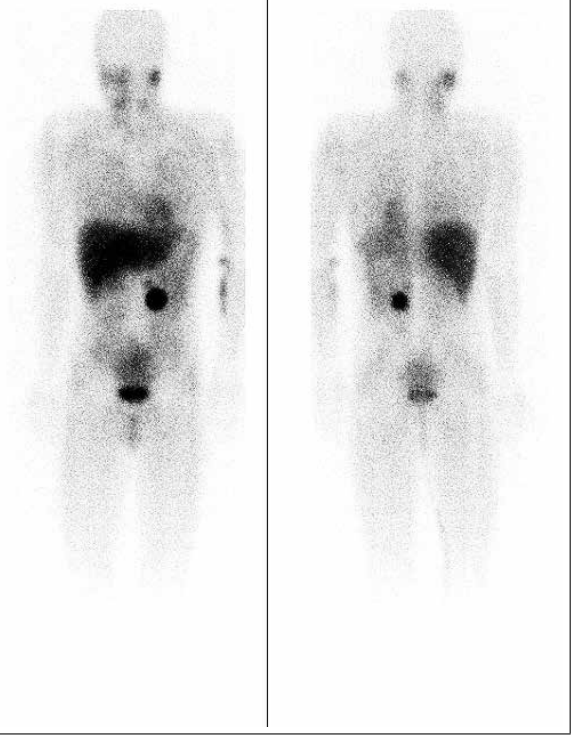
CASE REPORT

A 32-year-old male with an unremarkable medical history presented to the emergency department after an episode of aphasia, altered consciousness and confusion. He had recently experienced mild headaches. He was not using any medication or drugs. Physical examination at admission revealed no abnormalities; his blood pressure was 165/72 mmHg. After determination of this blood pressure, fundoscopy for papilloedema was not performed. He deteriorated, became aphasic and lost comprehension. Laboratory tests only revealed a slightly elevated white blood cell count of 10.2 x 10^9/l. A subsequently performed CT cerebrum showed no abnormalities, while lumbar puncture revealed an elevated lymphocyte count of 304/field. Under suspicion of viral encephalitis he was admitted to the neurology department and treated with broad-spectrum antibiotics and acyclovir. Elaborate tests for viral and bacterial infectious agents (cultures of blood and cerebrospinal fluid included) and autoimmune disease were negative. Electroencephalogram (EEG) showed complex partial seizures originating from the frontotemporal lobe on the left side. Despite anticonvulsant therapy he deteriorated again, with recurrence of the above-described symptoms. Repeated EEG showed frequent steep rhythmic delta activity in the left frontotemporal region with bradycardia: the episodes were due to complex, partial epileptic seizures. Subsequent MRI showed enhanced uptake of gadolinium in the frontal part of the meninges. Despite quadruple anticonvulsant therapy, the epilepsy was not adequately controlled, so he was transferred to the ICU for sedation and ventilation. Blood pressure levels during admission in the ICU in a sedated setting fluctuated within an

overall normal range. Maximum systolic pressure was 160 mmHg with a highest mean arterial pressure of 104 mmHg; these peak levels occurred in a short time interval. His therapy-resistant epilepsy was thought to be atypical and possibly due to paraneoplastic or limbic encephalitis. Therefore a CT scan of the head and neck, thorax, abdomen and pelvis was performed and showed three vascular lesions in the neck and two in the abdomen, both para-aortic. Twenty-four hour urinary excretion of norepinephrine (NE) and epinephrine collected in a sedated and ventilated setting was increased at 1.04 µmol/24 h (reference 0.04-0.47) and 0.19 µmol/24 h (reference 0-0.16), respectively; urinary excretion of metanephrines was normal. 123I-MIBG imaging showed increased uptake in the two abdominal extra-adrenal lesions *(figure 1)*. These hypervascular MIBG positive lesions were suggestive of multifocal paraganglioma. The patient was referred to the university hospital for laparoscopic removal of the two abdominal extra-adrenal paragangliomas, after preoperative alpha and beta blockade and intravenous hydration.

Removal was uneventful. Histology showed two localisations of a paraganglioma. Genetic testing showed an SDHD (Asp92Tyr) mutation on chromosome 11; SDHB immunostaining of paraganglioma tissue was compatible with the SDHD mutation. After surgery, NE excretion normalised and the anticonvulsant therapy could be discontinued. Almost two years after surgery the patient has not experienced any further epileptic activity.

Figure 1. *MIBG scan showing active paragangliomas*



This case shows a continuous state of epilepsy not responding to therapy in a patient with extra-adrenal catecholamine secreting paraganglioma. The epileptic seizures resolved after resection of the secreting paragangliomas and normalisation of catecholamine excretion. Since the head and neck paragangliomas were not resected, it was hypothesised that the increased level of catecholamines, especially NE, was associated with the seizures. Contradictory to this, it is well documented that the neurotransmitter NE has anticonvulsant properties.[6] Anticonvulsant drugs either deactivate neurons through the inhibitory neurotransmitter GABA or decrease the NE level in cerebrospinal fluid.[2,7]

However, NE also has proconvulsant properties under some conditions.[2] NE has an 'activating' role in the brain and can produce neural activity that may induce epilepsy, as reflected by the increased incidence of epilepsy after stressors.[8] The mechanism of action by which NE achieves its proconvulsant effects remains unclear. One hypothesis is that NE enhances cellular membrane potential by binding to its adrenoreceptors, consistent with the idea that NE increases the general excitability of neurons.[2] Due to an NE-secreting paraganglioma, NE levels increase systemically. The accompanying hypertension may lead to increased permeability of the blood-brain barrier to NE.[10] Another hypothesis postulates not direct activation of the cell membrane potential by NE but through a second messenger process, facilitating convulsions originating in those neurons.[2] Adrenoceptors are G protein coupled receptors that produce changes intracellularly at the level of cyclic AMP, after binding to NE.[2] A third possibility is activation of neurons participating in circuits that facilitate convulsions in non-adrenergic receptor bearing cells.[2] In addition vascular causes cannot be excluded. Elevated catecholamines can lead to cerebral ischaemia through vasospasm and provoke epileptic activity.[9]

When combining these proconvulsant and anticonvulsant hypotheses, we hypothesise that the elevation of NE might have played a role in the induction and maintenance of the continuous epileptic state in our patient. MRI scans of the brain were repeatedly normal. In the absence of hypertension, posterior reversible encephalopathy syndrome (PRES) was not considered. A paraneoplastic phenomenon was considered, despite negative tests for antibodies. But since removal of the metabolically active paragangliomas resolved his symptoms and the anticonvulsant medication could be stopped, this diagnosis was also rejected.

In conclusion, we believe this is the first case report in an adult patient showing a direct association between active paraganglioma leading to increased NE levels and epileptic seizures.

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