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Drug-resistant epilepsy, early-onset hypertension and white matter lesions: a hidden paraganglioma

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Full clinical cases submission template

TITLE OF CASE ***Do not include "a case report"***

Drug-resistant epilepsy, early-onset hypertension and white matter lesions: a hidden paraganglioma

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

We describe the case of a 35-year-old man with focal epilepsy since age 16. Due to a refractory course, several treatments were tried over the years, including insertion of a deep brain stimulator (DBS). At the time of his first assessment at our unit, he had recently been diagnosed with hypertension. An MR scan of brain revealed multiple T2 hyperintense white matter lesions, and evidence of previous haemorrhage in the left basal ganglia and pons. On follow-up imaging, the changes were considered to be in keeping with hypertensive arteriopathy. He was referred for further assessment of his hypertension and was found to have a para-aortic paraganglioma. This was excised 16 months after his initial presentation to us. The surgery was associated with an improvement in his seizure control. This case serves as a reminder of the need to be vigilant about the possibility of coexisting conditions in people with epilepsy.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Epilepsy is a common neurological disorder, with a worldwide lifetime prevalence of 7.6 per 1000.[1] In a quarter of people newly diagnosed with epilepsy, seizures persist despite appropriate medical treatment.[2] Among other factors, certain comorbidities are known to influence epilepsy prognosis,[3] and indeed comorbid conditions in epilepsy are common, with a cumulative prevalence of up to 50%.[3] This case illustrates the need to remain vigilant to the possibility of diverse other conditions in people with epilepsy, even in specialist settings and with established epilepsy diagnoses.

CASE PRESENTATION ***Presenting features, medical/social/family history***

A 35-year-old right-handed man was referred to a tertiary epilepsy centre for re-assessment of his refractory epilepsy. There was no family history of note. His antecedent history was unremarkable apart from two self-terminating febrile seizures before the age of 1 year. At age 16, he presented with two unprovoked generalised tonic–clonic seizures occurring within 24 hours. He started antiepileptic drug treatment, and subsequently his seizures have predominantly been focal cognitive seizures with impaired awareness. The latter have proved refractory to treatment, whilst his generalised tonic–clonic seizures have occurred only sporadically since the initiation of antiepileptic drugs.

An MR scan of brain and EEG, aged 20, were reported as normal. Scalp videotelemetry aged 22 failed to localise seizure onset. He underwent intracranial EEG recording on two occasions; first with bilateral temporal depth electrodes and later also with bilateral frontal and subfrontal strips. The final results suggested bilateral onset and he was not considered to be a candidate for resective surgery. A vagal nerve stimulator (VNS) was inserted aged 29. This proved ineffective and was subsequently switched off. Four years later, he underwent insertion of deep brain stimulator (DBS) electrodes to bilateral ventral anterior thalamic nuclei. Following DBS insertion, there was a change in his seizure semiology, with new types of brief episodes, 'drop attacks', during which he became vacant, his head deviated to the right and he would collapse. DBS also proved ineffective and was removed 3 years later.

On presentation at our centre, aged 35, his antiepileptic treatment was phenytoin, sodium

BMJ Case Reports

valproate, clobazam, levetiracetam and carbamazepine. He had previously also tried at least lacosamide, lamotrigine, topiramate, perampanel, and retigabine. However, he continued to experience daily drop attacks resulting in injuries. He carried an existing diagnosis of hypertension, for which he took perindropril. According to GP records, 'essential hypertension' was formally diagnosed 3 months before his presentation to us. His family recalled that at the time of DBS insertion 3 years before, his blood pressure was elevated, and attributed to 'white coat syndrome'.

INVESTIGATIONS ***If relevant***

He was admitted to our unit for investigations. Ambulatory EEG showed a slow background and interictal sharp activity with varying side emphasis. Several habitual seizures were captured, with EEG correlate of generalised spike wave discharge followed by a run of fast activity. Tachycardia was not reported in association with EEG changes or seizures. An MR scan of brain showed previous haemorrhage in the left basal ganglia and central pons, multiple T2-hyperintense lesions in the white matter of both hemispheres with a periventricular and peripheral distribution, and changes consistent with previous insertion and removal of DBS. His previous MR scans, the last preceding DBS insertion by 7 months, were reported as normal.

CSF examination showed only mildly elevated protein of 0.46 g/L (reference range 0.13-0.4) and a slightly increased CSF/serum albumin ratio of 7.33 (reference range <7.2). Screening for serum autoantibodies and antineuronal antibodies was negative. A repeat MR scan of brain 4 months after his admission showed new areas of T2 hyperintensity in the right basal ganglia, and two microhaemorrhages in the left thalamus and temporal lobe (Figure 1). He was reviewed by the neurovascular team: hypertensive arteriopathy was diagnosed, and treatment for hypertension was escalated with amlodipine.

Further multispecialty assessment revealed, 1 year after his admission, persistently elevated concentrations of fractionated normetadrenalines, with plasma normetadrenaline at 5880.1 pmol/L (reference range <1180.0). Plasma metadrenaline and 3-methoxytyramine concentrations were normal. Subsequent imaging, including abdominal SPECT/CT, demonstrated a partly calcified mass, anterior to the aorta and medial to the inferior vena cava, at the level of the L1/2 intervertebral disc. Metaiodobenzylguanidine (^{123}I-MIGB) scintigraphy was in keeping with a diagnosis of a paraganglioma.

DIFFERENTIAL DIAGNOSIS ***If relevant***

Differential diagnoses of DBS-related white matter change and of an inflammatory CNS disease were considered, but the absence of evidence in support of the latter, and the absence of reports of such MRI changes in association with DBS made further search for the cause of his MRI abnormalities necessary.

TREATMENT ***If relevant***

The patient underwent open surgery for the tumour 16 months after his initial presentation at our centre. The tumour measured 50x37x32 mm and was completely excised. Immunocytochemistry was positive for CD56 and chromogranin, confirming the diagnosis of paraganglioma. The Ki67 index was 10%. Apart from several foci of vascular invasion, there were no adverse histological features.

OUTCOME AND FOLLOW-UP

Following surgery, his metadrenaline concentrations returned to normal. In the ensuing 6 months, his blood pressure also normalised and antihypertensive treatment was stopped. The surgery was

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associated with significant improvement in his seizure frequency: at last follow-up, 8 months after surgery, he was experiencing seizures on 1–2 days per month in contrast to several times per week prior to surgery.

DISCUSSION ***Include a very brief review of similar published cases***

Paragangliomas are neuroendocrine tumours arising within the sympathetic or parasympathetic paraganglia. Sympathetic paragangliomas are derived from chromaffin cells and secrete catecholamines; histologically and functionally similar tumours arising from the adrenal medulla are historically known as phaeochromocytomas.[4,5] There is a significant genetic component, with an estimated 40% of tumours associated with germline mutations in one of several susceptibility genes, including *NF1*, *RET*, *VHL*, and the *SDHx* group of genes, which encode the subunits of succinate dehydrogenase.[4] Among the remaining sporadic cases, somatic mutations are recognised in a proportion of patients.[4] The prevalence of sympathetic paragangliomas/phaeochromocytomas among adults with hypertension is 0.2–0.6%.[6] In addition to episodic or sustained hypertension, patients may present with episodes of headache, sweating and palpitations.[5] Measurement of plasma free metanephrines or urinary fractionated metanephrines is a sensitive screening test, with positive results warranting imaging follow-up.[6] Although metastases are possible, especially in the context of mutations in *SDHB*, the majority of tumours are benign.[5] Surgical treatment, with appropriate preoperative medical management, is the mainstay of treatment.[6]

In keeping with the final diagnosis, our patient had hypertension and repeatedly elevated metadrenalines. In contrast, there was no history of episodic symptoms attributable to excess sympathetic activity; his habitual episodes were clinically and electrographically consistent with a diagnosis of epilepsy.

There are several accounts of seizures in the context of acute crises of phaeochromocytomas/paragangliomas.[7-9] In contrast, more prolonged disease courses appear less frequent. One group reported the case of an 8-year-old girl who presented with epilepsy and a right-sided cervical mass due to a carotid body tumour.[10] Excision of the tumour was performed 16 months after initial presentation, with complete remission of seizures. In this case, there was no evidence of excess of catecholamines, and although the authors postulated that intraoperative manipulation of the vagal nerve contributed to seizure remission, the origin of epilepsy remains unclear. In another case, a 7-year-old child was commenced on antiepileptic drugs following an acute presentation with headache, anxiety, palpitations, and unilateral tonic-clonic seizures; 2 years later, she was found to have an adrenal ganglioneuroma, with intraoperative crisis suggestive of catecholamine excess.[11] It is unclear what the course of the seizure disorder was prior to and following surgery.

Stress is associated with activation of the sympathetic adrenergic pathway of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis and is a commonly reported seizure trigger in people with epilepsy [12]. The relationship between catecholamines and seizures remains incompletely understood. Endogenous noradrenaline release from the locus coeruleus, as well as pharmacological agents leading to elevated extracellular concentrations of noradrenaline in the CNS, have been demonstrated to have anticonvulsant effects.[13] Among the adrenergic receptors, alpha receptors have higher affinity for noradrenaline. The most prevalent receptor type, $\alpha_{1A,}$ has been consistently shown to exert anticonvulsant effects, attributed to enhancement of gamma-aminobutyric acid (GABA)-mediated neurotransmission.[13] In contrast, for several other adrenergic receptors, evidence for effects of activation on seizure activity is less established, with evidence for pro-convulsant effects for some subtypes.[13] In the context of systemic excess of noradrenaline, consideration of the possible effects on seizure activity is further complicated by the fact that brain entry is prevented at the blood-brain barrier (BBB).[13] Noradrenaline-

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induced hypertension may, however, promote entry by means of induced BBB dysfunction.[13] In addition to other pro-convulsant effects associated with BBB dysfunction, it has been proposed that this could promote seizure activity by means of inhibition of endogenous noradrenaline release.[13]

Cerebral small vessel disease (SVD) is emerging as a risk factor for late-onset epilepsy,[14] and appears to be also associated with delayed seizures following symptomatic intracerebral haemorrhage.[15] In our patient, there was clear imaging evidence of vasculopathy and microhaemorrhages. While these appear to have developed much later than the onset of seizures, it is possible that these secondary effects of hypertension may have contributed to his epilepsy.

Of the genetic causes of paragangliomas, neurofibromatosis 1, caused by mutations in the *NF1* gene, is associated with seizures.[16] Our patient's phenotype was not in keeping with this syndrome. However, with the rapid increase in the knowledge of genetics of epilepsy,[17] it is possible that novel associations with other genetic conditions will be uncovered. From this perspective, the *SDHx* group of genes are especially interesting, given the links between succinate and GABA metabolism [18].

This patient with refractory epilepsy and a complex treatment history, including DBS, was found during the course of his evaluation to have new neuroimaging changes of unknown cause. Multispecialty assessments led to the diagnosis of hypertensive arteriopathy secondary to a sympathetic paraganglioma. Establishing the correct diagnosis was key to management, and led to improvement in seizure control.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

1. A paraganglioma is a possible cause of secondary hypertension in adults. Elevated concentrations of metadrenalines are a clue to diagnosis.

2. People with epilepsy frequently have other medical conditions, which may need evaluation in their own right.

3. Physicians looking after people with epilepsy have a critical role in identifying these conditions and ensuring appropriate investigations are arranged.

4. Management of comorbid conditions may lead to improvement in seizure control.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Figure 1. Left: T2-weighted MRI brain image from first admission at our unit, showing multiple white matter hyperintensities with a peripheral and periventricular distribution (blue arrows). Middle: on repeat imaging 4 months later, there is a new area of T2 hyperintensity in the head of the right caudate nucleus and in the anterior putamen (red arrow). Right: susceptibility weighted

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image performed on repeat MRI clearly demonstrates previous left basal ganglia haemorrhages (white arrow).

PATIENT'S PERSPECTIVE ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

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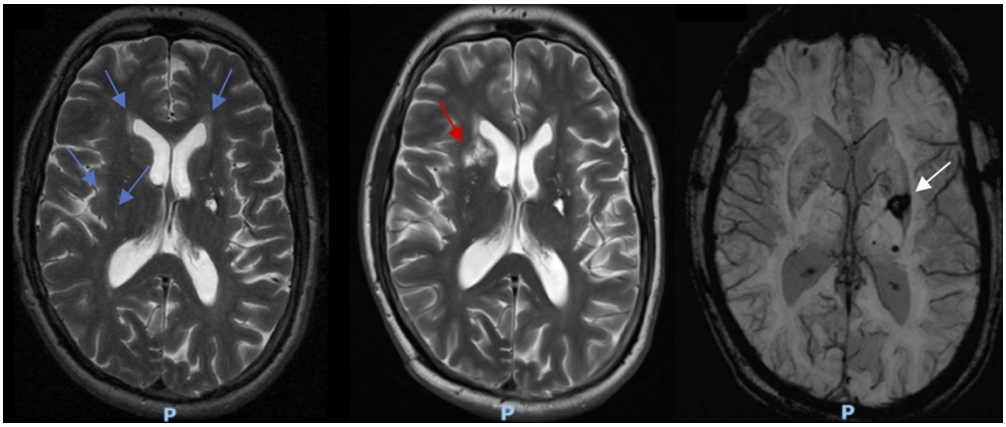

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