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THE GREAT PRETENDER: COULD A PHEOCHROMOCYTOMA MANIFEST ITSELF AS A SEIZURE?

Abstract: Epileptic seizures are defined as the transient appearance of signs or symptoms due to excessive or synchronous neuronal activity in the cerebral cortex. Pheochromocytomas and paragangliomas (PPGL) are tumors of chromaffin cells that arise from the medulla of the adrenal gland in 80-85% of patients and from the extra-adrenal sympathetic tissue of the abdomen, pelvis and chest in 10-20% of patients. The clinical picture of PPGL is variable and ranges from the absence of symptoms to severe clinical picture, depending on the biochemical profile. They are most often manifested by paroxysmal hypertension, followed by episodes of severe headache or diaphoresis, while epileptic attacks are rare. Neurological symptoms are present in many patients with PPGL. Also, paroxysmal neurological conditions such as vasodilating headache, intracranial tumors, diencephalic-autonomic epilepsy, hypertensive encephalopathy, focal arterial disease of the brain and anxiety state have been described, which may have similar clinical manifestations with pheochromocytomas. We present a 44-year-old woman, who has been diagnosed with pheochromocytoma as possible etiological basis of epileptic seizures. Pheochromocytoma, with its low incidence and "chameleon" clinical spectrum, should be considered as a potential etiological factor of convulsions.

Key words: Epileptic seizures, pheochromocytoma, norepinephrine

Introduction

Seizures are defined as transient occurrence of signs or symptoms due to the abnormally excessive or synchronous neuronal activity in the cerebral cortex (1). The International League Against Epilepsy (ILAE) has put forward the idea of etiology

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exploration in the new version of the ILAE position paper to pay more attention to searching for complicated spectrum of etiologies of seizures (2). Pheochromocytomas and paragangliomas (PPGL) are chromaffin cell tumors arising from the adrenal medulla in 80–85% of patients and from extra-adrenal sympathetic tissue of abdomen, pelvis and chest in 10–20% of patients (3). The clinical presentations of PPGL can be highly variable and range from even no symptom to severe symptoms, depending of biochemical profile, of which the most common manifestation is paroxysmal hypertension, accompanied with episodes of severe headache or diaphoresis, due to catecholamines excess (4, 5), while seizures are less common (6, 7). Neurological symptoms are present in many patients with PPGL. Varieties of neurological manifestations are described, including headache, perspiration, palpitation, and pallor in patients with PPGL and paroxysmal neurological conditions like vasodilating headache, intracranial tumor, diencephalic-autonomic epilepsy, hypertensive encephalopathy, focal arterial brain disease and anxiety state are easily to be confused with PPGL (8). PPGL has been referred to as ‘‘the great mimic’’ disease, the great pretender, making accurate clinical diagnosis of PPGL a difficult challenge (9). Seizures, though not so common, belong to the spectrum of possible manifestations.

Case report

A 44 years old woman was referred to University Clinic of Endocrinology by radiologist. Two years earlier she had syncopal crises during which she was referred to internal medicine specialist. She complained of headache, heart palpitation and malaise, occasionally had a feeling of heart palpitations and fatigue during exertion, as well as paroxysmal hypertension. The maximal self-measured blood pressure was 160/100 mmHg, the pulse is 90-100 beats per minute accompanied by heart pounding, sweating and a sense of panic. Abdominal US was performed, when a hyperechoic change with a diameter of 76 x 65mm was seen, then described in the right lobe of the liver, subcapsular, of benign characteristics. She was examined by a cardiologist, when blood pressure monitoring and ECG monitoring were performed (daily rhythm preserved, maximum value of TA during the day 141/100 mmHg, during the night the highest value 128/81 mmHg). Angiotensin converting enzyme inhibitors therapy was advised, which she did not take regularly. During the following year she had two commotional crises of consciousness in which she had spasms of the extremities with tongue bites. At the admission to Emergency Unit of Clinic of Neurology she was confused and did not remember the fall. Her vital signs were as follows: TA 140/80 mmHg, pulse 102 per min, temperature 36.9 C, respiratory rate 21 breathes per min. The biochemical analysis were within reference range. The physical examination was normal, except morsus linguae on the right side. She was treated with Phenobarbitone amp i. m. An urgent magnetic resonance imaging of the endocranium showed

supratentorial microangiopathic changes. Computer tomography of the endocranium showed no brain lesions. Subsequent EEG and EEG after sleep deprivation were done on several occasions. She had a non-specific slowing of FC on the right for 1-2 seconds. Lamictal was introduced according to the scheme with a gradual increase to 2 x100mg. Abdominal US showed a circular, clearly limited, hypoechoic, inhomogeneous change in the right adrenal gland size 119 x 94mm with peripheral and central vascularization. An MSCT of the abdomen was performed: in the right adrenal gland, a mass of size 124 x 90mm can be seen, with clear borders, pressing into the liver and pushing the right kidney, in wide contact with the VCI. No enlarged lymph nodes. She was referred to the Clinic of Endocrinology. The complete endocrine functional testing was done which excluded autonomous cortisol hypersecretion or functional tumors of adrenal cortex. Biochemical markers for tuberculosis and sarcoidosis were negative. The 24h urine was collected, after the appropriate diet, which confirmed a norepinephrine excess in 3 specimens. Adrenalin 48.3… 24.6… 39.9 nmol/24h (< 150), noradrenalin 957.2… 902.8… 944.3 nmol/24h (<570), dopamine 21.9.… 1900.5… 2296.7 nmol/24h (<3240) , metanephrine 0.10… 0.13… 0.10 µmol/24h(<1.4), normetanephrine 2.78… 9.14... 3.27 µmol/24h (< 3.45), 3 metoxytriptamine 1.27… 1.0… 1.27 µmol/24h (<1.0). Calcitonin (CT): 7; Carcinoembrionic antigen (CEA): < 1.73; Chromogranin A 1342.6 … 0.45 ng/ml. The genetic analysis was taken for multiple endocrine neoplasia. Radiography of the heart and lungs: No definite signs of infiltration and consolidation in the lung parenchyma were seen. MR examination of the abdomen: In the right hemiabdomen, a large tumoral change of the origin of the right adrenal gland can be observed, measuring 96 x 90 x 140mm, well-defined, with compression on the surrounding structures that it adheres and suppresses. The mass is pressed into the right lobe of the liver, compresses the VCI in a longer segment of about 80 mm, occludes the right renal tract caudally, but without certain MR signs of infiltration of the surrounding structures. The left adrenal gland has normal MR tissue characteristics. Diagnosis of noradrenaline secreting pheochromocytoma was made. We administered long acting alpha blocking agent preoperatively, adding beta blocking therapy after the achievement of preoperatively adequate heart rate and blood pressure parameters. The complete surgical excision of the right adrenal mass was done through an open posterior approach. The postoperative course was uneventful. The patient was discharged on 10th postoperative day in a good condition with a scheduled follow up. Macroscopic findings: Tumor of the right adrenal gland, mass 440g, dimensions 140 x 100 x 70 mm, brown color, solid cut surface, soft consistency. Adrenal gland dimensions 40 x 25 x 3 mm. Microscopic findings: The tumor is made up of polygonal cells, eosinophilic cytoplasm, which are arranged in nests separated by a delicate fibrovascular stroma. Tumor cells are: Chromogranin A +, S100 +, SDHB + S. Sustentacular cells are rare, single. Adrenal gland without significant PH changes. Large nests or diffuse type of growth (>10% tumor volume):

2. Adrenal Gland Scale Score (PASS) score: 5. Proliferative index Ki67: 5%. Pathohistological diagnosis: *Pheochromocytoma glandulae suprarenalis*. During the follow up, 2 months after the surgery, Imaging of the whole body and tomography (structural and functional imaging) of the abdomen and pelvis were performed 24 hours after slow iv. injection 140.6 MBq mI (J123) BG: physiological distribution. Catecholamines in the urine specimens were negative, chromogranin A in the reference range. FDG PET: Focal zones of elevated glucose metabolism are not shown, which would reliably indicate FDG-active disease. The last EEG after sleep deprivation performed 3 months postoperatively was described as normal. The patient had no headache or seizure. The neurologist suggested to continue with the therapy she is taking Lamictal a 100mg+0+100mg as before. The endocrine follow-up is planned every 3 months during the first year after the surgery.

Discussion

PPGLs have a notable ability of boosting norepinephrine (NE) levels systemically, what's more, hypertension, the most common sign of PPGL could facilitate the permeability of blood brain barrier to NE (10). It has been clearly demonstrated by Clinckers and his colleagues that a1A-AR stimulation and a1D-AR antagonism can inhibit seizures associated with respectively significant hippocampal GABA increases and GLU decreases (11). The inhibitory effects of NA on epileptogenesis was further validated (12). There is also indirect evidence, for example, vagus nerve stimulation (VNS) known to conduct its anticonvulsive effect through increasing NA levels in the hippocampus in limbic seizures (13). Additionally, coadministration of β-ARs ligands can augment the effects of traditional antiepileptic drugs like diazepam, phenobarbital, lamotrigine and valproate (14-16). Controversially, more and more studies have certified the proconvulsive effect of NE, which were well exhibited in the review written by Paul J. Fitzgerald (17). A series of studies about beta-blockers conducted by different researchers in different times seemed to be typical evidence supporting the proconvulsive effect of NE. Some beta-blockers, such as metoprolol, showed some protective effects against audio seizures (14). As for the question of how NE played its proconvulsant roles, there are several significant mechanisms. As a classical ''stress factor'', NE can powerfully agitate cortical neurons mainly in two pathways (18). NE activates α2-adrenergic receptors in the prefrontal cortex and hyperpolarization-activated cyclic nucleotide gated channels (HCN) closed by a reduced level of intracellular cyclic adenosine monophosphate (cAMP), which decreases the threshold of neuronal membrane potential (19, 20). On the other hand, NE suppresses Ca2+ activated K+ channels (SK) and its after-hyperpolarization conductance in a cAMP and PKA dependent pathway by binding with b-adrenergic receptor, which assists the spread of the neurons' action potentials (21-24). Since NE plays a powerful activating role on

neurons, it is apprehensible that excessive elevation of neural activity may result in seizures or epilepsy. The study conducted by Szot et al. suggests that α2-AR agonism produces its proconvulsant effect through presynaptic α2-AR and its anticonvulsant effect through postsynaptic α2-AR (25). As for the anticonvulsant effects of β2-AR, which have not been attested in all the relevant studies, a reasonable explanation would be that endogenous NE does not activate β2-AR under physiological conditions, while exogenous NE activates β2-AR, producing its anticonvulsant effect (26). As Paul J. Fitzgerald has proposed in his review after examining hundreds of studies, there is a chance that NE plays its anticonvulsant property at an appropriate concentration but has a proconvulsant effect in either too high or too low concentrations (27). The ultimate conclusions of the different studies depended on the animal species, the strain, the model of epilepsy employed and also receptor location (27).

Conclusion

The definite pathogenetic mechanisms explaining how PPGL can cause seizures are far from being clearly understood. Li et al but by reviewing numerous studies and case reports in this field, postulated pathological mechanisms as follows: 1. hypertensive encephalopathy (HTE) due to the elevated catecholamine secreted by PPGL plays a central part in the process of posterior reversible encephalopathy syndrome (PRES), with which seizures, especially generalized tonic-clonic activity, are commonly accompanied; 2. seizures are not a common clinical feature but do exist in patients with reversible cerebral vasoconstriction syndrome (RCVS), which is tightly related to sympathetic overactivity caused by many factors including the PPGL itself and catecholamines; 3. during the process of cerebral ischemia or infarction caused by PPGL in many ways, ion disturbance owing to the inactivation of ATP-dependent ion pumps and other causes including hypoxia, metabolic dysfunction, global hypoperfusion, hyperperfusion, glutamate excitotoxicity and BBB disruption have effects on the hypersynchronous discharges of neurons; 4. NE applies its excitatory effects on neurons by modulation of SK or HCN channels and excessive elevation of neural activity may result in seizures or epilepsy (28). Pheochromocytoma, along with its low incidence and clinical spectrum of "the great pretender" should be considered as a possible etiological factor of seizures.

References

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizure and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005; 46: 470–2.

2. Ingrid E, Scheffer. Samuel Berkovic, Giuseppe Capovilla et. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58(4): 512–21.
3. De Lellis RA, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization Classification Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs. Lyon, France: IARC Press; 2004, pp. 147– 66.
4. Angeli A, Osella G, Ali A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. Horm Res 1997; 47(4–6): 279–83.
5. Kebebew E, Siperstein AE, Clark OH, Duh QY. Results of laparoscopic adrenalectomy for suspected and unsuspected malignant adrenal neoplasms. Arch Surg 2002; 137(8): 948–53.
6. Anderson NE, Chung K, Willoughby E, Croxson MS. Neurological manifestations of phaeochromocytomas and secretory paragangliomas: appraisal. J Neurol Neurosurg Psychiatry 2013; 84(4):452–7.
7. Scully RE, Mark EJ, McNeely WV, McNeely BU. Case records of the Massachusetts General Hospital, Case 15-1988. N Engl J Med 1988; 318: 970.
8. Thomas JE, Rooke ED, Kvale WF. The neurologist's experience with pheochromocytoma. A review of 100 cases. JAMA 1966; 197: 754–8.
9. Manger WM. The vagaries of pheochromocytomas. Am J Hypertens 2005; 18: 1266–70.
10. Hardebo JE, Owman C. Barrier mechanisms for neurotransmitter monoamines and their precursors at the blood–brain interface. Ann Neurol 1980; 8: 1–31.
11. Clinckers R, Zgavc T, Vermoesen K, Meurs A, Michotte Y, Smolders I. Pharmacological and neurochemical characterization of the involvement of hippocampal adrenoreceptor subtypes in the modulation of acute limbic seizures. J Neurochem 2010; 115: 1595–607.
12. Micheletti G, Warter JM, Marescaux C, Depaulis A, Tranchant C, Rumbach L, et al. Effects of drugs affecting noradrenergic neurotransmission in rats with spontaneous petit mal-like seizures. Eur J Pharmacol 1987; 135: 397–402.
13. Raedt R, Clinckers R, Mollet L, Vonck K, El Tahry R, Wyckhuys T, et al. Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. J Neurochem 2011; 117: 461–9.
14. De Sarro G, Di Paola ED, Ferreri G, De Sarro A, Fischer W. Influence of some beta-adrenoceptor antagonists on the anticonvulsant potency of antiepileptic drugs against audiogenic seizures in DBA/2 mice. Eur J Pharmacol 2002; 442: 205–13.
15. Fischer W. Anticonvulsant profile and mechanism of action of propranolol and its two enantiomers. Seizure 2002; 11: 285–302.
16. Luchowska E, Luchowski P, Wielosz M, Kleinrok Z, Czuczwar SJ, Urbanska EM. Propranolol and metoprolol enhance the anticonvulsant action of valproate and diazepam against maximal electroshock. Pharmacol Biochem Behav 2002; 71: 223–31.
17. Fitzgerald P. Is elevated norepinephrine an etiological factor in some cases of epilepsy? Seizure 2010; 19: 311–8.

18. McCormick DA. Neurotransmitter actions in the thalamus and cerebral cortex. J Clin Neurophysiol 1992; 9: 212–23.
19. Barth AM, Vizi ES, Zelles T, Lendvai B. Alpha2-adrenergic receptors modify dendritic spike generation via HCN channels in the prefrontal cortex. J Neurophysiol 2008; 99: 394–401.
20. Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, et al. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell 2007; 129: 397–410.
21. Haas HL, Rose GM. Noradrenaline blocks potassium conductance in rat dentate granule cells in vitro. Neurosci Lett 1987; 78:171–4.
22. Sah P, French CR, Gage PW. Effects of noradrenaline on some potassium currents in CA1 neurones in rat hippocampal slices. Neurosci Lett 1985; 60: 295–300.
23. Sah P, Isaacson JS. Channels underlying the slow after hyperpolarization in hippocampal pyramidal neurons: neurotransmitters modulate the open probability. Neuron 1995; 15: 435–41. 502 revueneurologiq 1 7 5 (2 0 1 9) 4 9 5 – 5 0 5
24. Pedarzani P, Storm JF. PKA mediates the effects of monoamine transmitters on the K+ current underlying the slow spike frequency adaptation in hippocampal neurons. Neuron 1993; 11: 1023–35.
25. Szot P, Lester M, Laughlin ML, Palmiter RD, Liles LC, Weinshenker D. The anticonvulsant and proconvulsant effects of alpha2-adrenoreceptor agonists are mediated by distinct populations of alpha2A-adrenoreceptors. Neuroscience 2004; 126: 795–803.
26. Weinshenker D, Szot P, Miller NS, Palmiter RD. Alpha (1) and beta (2) adrenoreceptor agonists inhibit pentylenetetrazole -induced seizures in mice lacking norepinephrine. J Pharmacol Exp Ther 2001; 298: 1042–8.
27. Fitzgerald P. Is elevated norepinephrine an etiological factor in some cases of epilepsy? Seizure 2010; 19: 311–8.
28. Li Y, Zhang B. Seizures in patients with a phaeochromocytoma/paraganglioma (PPGL): A review of clinical cases and postulated pathological mechanisms. Rev Neurol (Paris). 2019 Oct;175(9): 495–505.