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FEOHROMOCITOM KAO POTENCIJALNI UZROK NAPADA EPILEPSIJE

Sažetak: Epileptični napadi se definišu kao prolazna pojava znakova ili simptoma usled prekomerne ili sinhrone neuronske aktivnosti u moždanoj kori. Feohromocitomi i paragangliomi (PPGL) su tumori hromafinih ćelija koji nastaju iz medule nadbubrežne žlezde kod 80–85% pacijenata i iz ekstraadrenalnog simpatičkog tkiva abdomena, karlice i grudnog koša kod 10–20% pacijenata. Klinička slika PPGL je varijabilna i kreće se od odsustva simptoma do teške kliničke slike, u zavisnosti od biohemijskog profila. Najčešće se manifestuju paroksizmalnom hipertenzijom, praćenom epizodama jake glavobolje ili dijaforeze, dok su epi napadi retki. Neurološki simptomi su prisutni kod mnogih pacijenata sa PPGL. Takođe, opisana su paroksizmalna neurološka stanja, kao što su vazodilatirajuća glavobolja, intrakranijalni tumori, diencefalno-autonomna epilepsija, hipertenzivna encefalopatija, fokalna arterijska bolest mozga i stanje anksioznosti, koja mogu imati slične kliničke manifestacije sa feohromocitomima. Prikazujemo ženu uzrasta 44 godine, kod koje postoji mogućnost da je dijagnostikovani feohromocitom u etiološkoj osnovi epileptičnih napada. Feohromocitom, uz njegovu nisku incidenciju i klinički spektar „kameleona“ treba posmatrati kao potencijalni etiološki faktor konvulzija.

Ključne reči: epileptični napadi, feohromocitom, norepinefrin

Uvod

Epileptični napadi se definišu kao prolazna pojava znakova ili simptoma usled prekomerne ili sinhrone neuronske aktivnosti u moždanoj kori (1). International Leauge Against Epilepsy (ILAE) je naglasila značaj etiološke komponente u cilju rasvetljavanja komplikovanog spektra uzroka epi napada (2). Feohromocitomi i paragangliomi (PPGL) su tumori hromafinih ćelija koji nastaju iz medule nadbubrežne

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žlezde kod 80–85% pacijenata i iz ekstraadrenalnog simpatičkog tkiva abdomena, karlice i grudnog koša kod 10–20% pacijenata (3). Klinička slika PPGL je veoma varijabilna i kreće se od odsustva simptoma do teške kliničke slike, u zavisnosti od biohemijskog profila. Najčešće se manifestuju paroksizmalnom hipertenzijom, praćenom epizodama jake glavobolje ili dijaforeze (4, 5), dok su epi napadi retki (6, 7). Neurološki simptomi su prisutni kod mnogih pacijenata sa PPGL. Takođe, opisana su paroksizmalna neurološka stanja, kao što su vazodilatirajuća glavobolja, intrakranijalni tumor, diencefalno-autonomna epilepsija, hipertenzivna encefalopatija, fokalna arterijska bolest mozga i stanje anksioznosti, koja mogu imati slične kliničke manifestacije sa PPGL-om (8). S obzirom na širok spektar kliničke slike, klinička sumnja na PPGL na osnovu neuroloških manifestacija je izazovna (9).

Prikaz slučaja

Žena, uzrasta 44 godine, upućena je od strane radiologa u Univerzitetsku kliniku za endokrinologiju, dijabetes i bolesti metabolizma. Dve godine ranije imala je sinkopalne krize tokom kojih je upućena specijalisti interne medicine. Žalila se na glavobolju, lupanje srca i malaksalost, povremeno je imala osećaj lupanja srca i umora pri naporu, kao i paroksizmalnu hipertenziju. Maksimalni samostalno izmeren krvni pritisak bio je 160/100 mmHg, puls 90–100 otkucaja u minuti, praćen lupanjem srca, znojenjem i osećanjem panike. Urađena je UZ vizuelizacija abdomena, kada je uočena hiperehogena promena prečnika 76 x 65mm, opisana u desnom režnju jetre, subkapsularna, benignih karakteristika. Učinjen je 24h monitoring krvnog pritiska (dnevni ritam očuvan, maksimalna vrednost TA tokom dana 141/100 mmHg, tokom noći najveća vrednost 128/81 mmHg). Savetovana je terapija inhibitorima angiotenzin konvertujućeg enzima, koju nije redovno uzimala. Tokom naredne godine imala je dve komocionalne krize svesti u kojima je imala grčeve ekstremiteta sa ugrizom jezika. Na prijemu u Urgentni centar UKCS bila je konfuzna i nije se sećala pada. Vitalni znaci na prijemu: TA 140/80 mmHg, puls 102 u minuti, temperatura 36,9 C, frekvencija disanja 21 u minuti. Biohemijske analize su bile u referentnom opsegu. Fizički pregled je bio normalan, osim morsus linguae na desnoj strani. Th: Fenobarbiton amp I i. m. Hitna magnetna rezonanca endokranijuma pokazala je supratentorijalne mikroangiopatske promene. Kompjuterska tomografija (MSCT) endokranijuma nije pokazala lezije mozga. Naknadni EEG i EEG nakon deprivacije sna rađeni su u nekoliko navrata – nespecifično usporavanje FC desno 1–2 sekunde. Lamictal je uveden prema šemi sa postepenim povećanjem do 2 x 100 mg. UZ abdomena je pokazao kružnu, jasno ograničenu, hipoehogenu, nehomogenu promenu u desnoj nadbubrežnoj žlezdi veličine 119 x 94 mm sa perifernom i centralnom vaskularizacijom. MSCT abdomena: u desnoj nadbubrežnoj žlezdi masa veličine 124 x 90 mm, jasnih granica, pritiska jetru i desni bubreg, u širokom kontaktu sa VCI. U Univerzitetskoj klinici

za endokrinologiju učinjeno je kompletno funkcionalno testiranje koje je isključilo autonomnu hipersekreciju kortizola ili funkcionalne tumore kore nadbubrežne žlezde. Biohemijski markeri za tuberkulozu i sarkoidozu su bili negativni. Sakupljen je 24h urin, nakon odgovarajuće dijete, što je potvrdilo hipersekreciju norepinefrina u 3 uzorka. Adrenalin 48,3… 24,6… 39,9 nmol/24h (< 150), noradrenalin 957,2… 902,8… 944,3 nmol/24h (< 570), dopamin 21,9… 1900,5… 2296,7 nmol/ (< 3240) metanefrin 0,10… 0,13… 0,10 μmol/24h (< 1,4), normetanefrin 2,78.… 9,14… 3,27 μmol/24h (< 3,45), 3 metoksitriptamin 1,27… 1,0… 1,27 μmol/24h (< 1,0). Kalcitonin (CT): 7 ng/l; Karcinoembrionalni antigen (CEA): < 1,73; Hromogranin A: 1342.6 ng/ml. Ostale hormonske analize urednog nalaza. Uzorak krvi upućen je na genetsku analizu za multiplu endokrinu neoplaziju. Radiografija srca i pluća: uredan nalaz. MR pregled abdomena urađen je u aksijalnoj, koronarnoj i sagitalnoj ravni uz primenu iv. kontrasta. U desnom hemiabdomenu uočava se tumorska promena porekla desne nadbubrežne žlezde, dimenzija 96 x 90 x 140mm, sa kompresijom na okolne strukture koje potiskuje. Utisnuta je u desni režanj jetre, komprimuje VCI u segmentu od oko 80 mm, ali bez MR znakova infiltracije okolnih struktura. Perifokalno oko same promene je laminarni sloj slobodne tečnosti. Leva nadbubrežna žlezda ima normalne karakteristike MR tkiva. Ostali nalaz uredan. Postavljena je dijagnoza noradrenalin sekretujućeg feohromocitoma. Preoperativno pripremana dugo delujućim alfa blokatorima, uz terapiju beta blokatorima nakon postizanja preoperativno adekvatnih parametara srčane frekvencije i krvnog pritiska. Kompletna hirurška ekscizija mase desne nadbubrežne žlezde urađena je otvorenim zadnjim pristupom. Postoperativni tok je protekao bez komplikacija. Makroskopski nalaz: Tumor desne nadbubrežne žlezde, mase 440 g, dimenzija 140 x 100 x 70 mm, braon boje, čvrste površine reza, meke konzistencije. Dimenzije nadbubrežne žlezde 40k25k3mm. Mikroskopski nalazi: Tumor se sastoji od poligonalnih ćelija, eozinofilne citoplazme, koje su raspoređene u gnezda odvojena delikatnom fibrovaskularnom stromom. Tumorske ćelije: hromogranin A +, S100 +, SDHB + S. Sustentakularne ćelije su retke, pojedinačne. Nadbubrežna žlezda bez značajnih promena PH. Velika gnezda ili difuzni tip rasta (> 10% zapremine tumora). Ocena na skali nadbubrežne žlezde (PASS): 5. Proliferativni indeks Ki67: 5%. Patohistološka dijagnoza: Pheochromocitoma glandulae suprarenalis. Tokom praćenja, 2 meseca nakon operacije, urađena je scintigramska vizuelizacija abdomena i male karlice 24 sata nakon i.v. aplikacije140,6 MBk Mi (J123) BG. Dobijeni scintigrami pokazuju fiziološku distribuciju. Kateholamini u uzorcima urina bili su negativni, hromogranin A u referentnom opsegu. FDG PET: Fokalne zone povišenog metabolizma glukoze nisu prikazane, što bi pouzdano ukazivalo na FDG-aktivnu bolest. Poslednji EEG nakon deprivacije sna urađen 3 meseca postoperativno je opisan kao normalan. Pacijentkinja je negirala prethodne tegobe. Neurolog je predložio da se nastavi sa terapijom koju uzima, Lamictal 100mg+0+100mg. Analize genetskog ispitivanja nisu pristigle. Endokrinološko praćenje je planirano na 3 meseca tokom prve godine nakon operacije.

Diskusija

PPGL imaju značajnu sposobnost sistemskog povećanja nivoa norepinefrina (NE). Štaviše, hipertenzija, najčešći znak PPGL-a, može per se povećati propustljivost krvno-moždane barijere za NE (10). Clinckers i kolege su jasno pokazali da α1A-AR stimulacija i antagonizam α1D-AR mogu inhibirati napade povezane sa značajnim povećanjem GABA u hipokampusu i smanjenjem GLU (11). Inhibicijski efekti NA na epileptogenezu dalje su potvrđeni u studijama na malim životinjama (12). Postoje i indirektni dokazi: stimulacija vagusnog nerva (VNS), koja ostvaruje svoj antikonvulzivni efekat kroz povećanje nivoa NA u hipokampusu kod limbičkih napada (13). Pored toga, istovremena primena β-AR liganda može povećati efekte tradicionalnih antiepileptičkih lekova kao što su diazepam, fenobarbital, lamotrigin i valproat (14–16).

Kontroverzno, sve više i više studija potvrđuje prokonvulzivni efekat NE, što je prikazao u recenziji Paul J. Fitzgerald (17). Niz studija o beta-blokatorima, koje su sproveli različiti istraživači, mogu se posmatrati kao jasan dokaz koji podržava prokonvulzivni efekat NE. Neki beta-blokatori, kao što je metoprolol, pokazali su protektivne efekte u slučajevima zvučno provociranih konvulzija (14). Odgovor na pitanje kako NE ostvaruje prokonvulzivnu ulogu nalazi se u nekoliko značajnih mehanizama. Kao klasični „stresogeni faktor“, NE može snažno agitirati kortikalne neurone na dva načina (18). NE aktivira α2-adrenergičke receptore u prefrontalnom korteksu i hiperpolarizacijom aktiviranim cikličnim nukleotidnim kanalima (HCN) zatvorenim smanjenim nivoom intracelularnog cikličnog adenozin monofosfata (cAMP), što smanjuje prag potencijala neuronske membrane (19, 20). S druge strane, NE suprimira Ca2+ aktivirane K+ kanale i njihovu provodljivost nakon hiperpolarizacije u cAMP i PKA (protein kinaza A) zavisnom putu vezujući se za β-adrenergički receptor, koji pomaže širenju akcionih potencijala neurona (21–24). Pošto NE igra moćnu aktivirajuću ulogu na neuronima, razumljivo je da prekomerno povećanje neuralne aktivnosti deluje proepileptogeno.

Studija koju su sproveli Szot et al. sugeriše da α2-AR agonizam ostvaruje svoj prokonvulzivni efekat preko presinaptičkog α2-AR, a svoj antikonvulzivni efekat kroz postsinaptički α2-AR (25). Što se tiče antikonvulzivnih efekata na β2-AR, koji nisu potvrđeni u svim relevantnim studijama, razumno objašnjenje bi bilo da endogeni NE ne aktivira β2-AR u fiziološkim uslovima, dok egzogeni NE aktivira β2-AR, proizvodeći njegov antikonvulzan efekat (26). Kao što je Paul J. Fitzgerald predložio, nakon ispitivanja stotina studija, postoji mogućnost da NE ostvaruje svoje antikonvulzivno svojstvo u odgovarajućoj koncentraciji, ali ima prokonvulzivni efekat u previsokim ili preniskim koncentracijama (27). Krajnji zaključci različitih studija zavisili su od životinjske vrste, soja, korišćenog modela epilepsije i lokacije receptora (27).

Zaključak

Definitivni patogenetski mehanizmi koji objašnjavaju kako PPGL mogu provocirati epileptične napade daleko su od jasnog razumevanja. Li i saradnici, pregledom brojnih studija o slučajevima u ovoj oblasti, pretpostavili su sledeće patološke mehanizme: 1. Hipertenzivna encefalopatija (HTE), zbog povišenih kateholamina koje luči PPGL, igra centralnu ulogu u procesu sindroma zadnje reverzibilne encefalopatije (engl. posterior reversible encephalopathy, PRES), koji je obično praćen generalizovanom toničko-kloničkom aktivnošću; 2. Epileptične konvulzije nisu uobičajena klinička karakteristika, ali postoje kod pacijenata sa sindromom reverzibilne cerebralne vazokonstrikcije (RCVS), koji je usko povezan sa prekomernom aktivnošću simpatikusa uzrokovanom različitim faktorima, uključujući PPGL; 3. Tokom procesa cerebralne ishemije ili cerebralnog infarkta izazvanog PPGL-om , poremećaj jona usled inaktivacije ATP-zavisnih jonskih pumpi i drugi uzroci, uključujući hipoksiju, metaboličku disfunkciju, globalnu hipoperfuziju, ekscitotoksičnost glutamata i poremećaj BBB imaju ulogu u hipersinhronim pražnjenjima neurona; 4. NE ostvaruje svoje ekscitatorne efekte na neurone modulacijom SK ili HCN kanala i prekomerno povećanje neuralne aktivnosti može dovesti do konvulzija (28). Feohromocitom, uz njegovu nisku incidenciju i klinički spektar „kameleona“ treba posmatrati kao potencijalni etiološki faktor konvulzija.

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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.

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