Schizophrenia Research 176 (2016) 304–306

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Cases of remission of psychosis following resection of pheochromocytoma or paraganglioma

James S. Brown Jr. MD, MPH, MS [1]

VCU School of Medicine, Department of Psychiatry, Richmond, VA, United States

ARTICLE INFO

Article history:
Received 26 July 2016
Received in revised form 8 August 2016
Accepted 11 August 2016
Available online 14 August 2016

Keywords:
Psychosis
Schizophrenia
Pheochromocytoma
Paraganglioma
Tumor
Cancer

ABSTRACT

The author previously proposed that schizophrenia has similar cytokine expression compared to melanoma, a neural crest cell tumor. One possible tumor model of schizophrenia includes anti-NMDA receptor encephalitis, a paraneoplastic syndrome. While examining the possible relationship of neural crest cell tumors to schizophrenia, the author found several case reports of psychosis resulting from pheochromocytomas and paragangliomas, types of neural crest cell tumors that secrete catecholamines. In most cases, surgical resection of the tumors resulted in remission of psychotic symptoms, and some remissions were associated with reduced levels of peripheral catecholamine levels. These reports suggest, first, that the differential diagnosis of psychosis with autonomic instability should include these tumors. Second, the cases raise a theoretical question as to how these tumors might cause psychosis. On one hand, the elevated peripheral catecholamines caused by these tumors generally agree with aspects of the dopamine hypothesis of schizophrenia although the mechanism of how peripheral dopamine would cause psychosis is unknown. On the other hand, these tumors could possibly secrete an unidentified antibody to a receptor similar to what is observed in anti-NMDA receptor encephalitis.

1. Introduction

The author previously proposed a tumor model of schizophrenia based on similar expressions of interferon-γ, tumor necrosis factor-α, and interleukin in schizophrenia and cancer (Brown, 2016). At least two scenarios could explain how a tumor might cause psychosis. The first was autoimmune anti-*N*-methyl-D-aspartate (NMDA)-receptor encephalitis (NMDAR-E), a type of paraneoplastic syndrome attributed to ovarian and other tumors associated with both bipolar and psychotic disorders (Dalmau et al., 2008; Leon-Caballero et al., 2015). The second was based on the similarity of schizophrenia to melanoma as the two conditions not only share cytokine expressions but also hallmarks and characteristics of cancer. Melanocytes, the cancerous cells of melanoma, originate embryonically from the neural crest from which numerous cell types also emerge including cells of the adrenal medullary and the peripheral nervous system from which pheochromocytomas (PC) and paragangliomas (PA) develop respectively. While investigating these tumors, the author located several reports of remitted psychosis following surgical resection of PC or PA that have not been previously collated. Interestingly, these tumors are known to secrete dopamine along with other catecholamines.

2. Cases

The earliest report of PC associated with psychosis was in 1960 when Pratt (Pratt, 1973) described cases of familial carotid body tumors (a type of PA) associated with psychosis. No additional information regarding psychosis was provided for these cases. The next reported case in 1969 was of a 32-year-old man initially presenting with insomnia and abdominal fullness and diagnosed with schizophrenia (Lulu, 1969). Following more than one hospitalization including electroshock treatment (ECT) which resolved symptoms and allowed discharge, he was later re-admitted with extreme agitation accompanied by headache, chest pain, tenseness and abdominal fullness. These symptoms were retrospectively attributed to a PC of the organs of Zuckerkandl that secreted excessive catecholamines. The PC was diagnosed after extreme hypertension and tachycardia occurred during a surgical procedure unrelated to the psychiatric admission. On assessment for PC, the patient had a 24-hour urinary total catecholamine concentration of 1770 μg (normal 8–160 μg). Following excision of the tumor, his psychiatric symptoms remitted and catecholamine levels returned to normal. This was an isolated case, and it was not until 1977 that Manger (Manger and Gifford, 1977) (p.142) reported a case of non-familial PC with psychosis that resolved with surgery, and another case of paranoid psychosis resulting from metastatic PC.

A case of PC in a 35-year-old woman with no prior psychiatric history confirms the association of urinary catecholamines with psychotic symptoms (Bahemuka, 1983). Cerebrospinal fluid Wassermann and

E-mail address: jbrown2185@aol.com.
[1] Mailing Address: c/o P.O. Box 622 Midlothian, VA 23113, United States.

http://dx.doi.org/10.1016/j.schres.2016.08.012
0920-9964/

Kahn reactions, protein, gammaglobulins, cultures and white cell count were negative or normal. Blood Wassermann and Kahn reactions and culture were negative or normal. Following a month history of palpitations, sweating, dizziness and headache, the patient developed anxiety, paranoia and auditory hallucinations. Total 24-hour urinary catecholamines ranged from 769 to 900 μg (normal up to 180 μg) during symptoms, and fell to 97–112 μg post-operatively. All psychiatric symptoms resolved following surgery. The laboratory investigations in this case indicate that antineuronal antibodies were not likely the cause of the psychiatric symptoms.

ECT, as described above, does improve psychotic symptoms from PC but is an absolute contraindication in known cases as ECT can lead to fatal cardiac arrest due to excess catecholamine release stimulated from the tumor by electroshock and possibly, some anesthetics (Drake and Ebaugh, 1956). Carr and Woods (Carr and Woods, 1985) reported a 27-year-old man with psychotic depression treated with ECT whose blood pressure suddenly rose to 260/190 during the procedure but without fatal consequences. With further ECT treatments with blood pressure control, his mental condition improved. Subsequently he was found to have elevated metanephrine excretion (19 mg/24 h, high normal 1.8 mg/24 h) and was diagnosed with PC. Pre-ECT the patient had been mildly hypertensive (140/90) but otherwise the tumor was clinically "silent." Post-operatively the patient remained psychiatrically stable. In this particular case, the psychiatric symptoms resolved with ECT so the remission of symptoms that remained after surgical resection of the PC could have resulted entirely from the ECT and/or from the surgery.

Pheochromocytoma can also present with psychosis as the initial symptom as described in a case of a 35-year-old man with no prior psychiatric history (Benabarre et al., 2005). Symptoms resolved with olanzapine although over the following 2 years he experienced a total of 8 psychotic episodes. Eventually the patient developed a hypertensive episode with palpitations, anxiety, sweating and chest pain and was found to have elevated catecholamines (values not reported). Surgical resection of a PC detected by computed tomography (CT) resulted in sustained remission of psychiatric symptoms.

A case of a 17-year-old female who presented with headaches, amenorrhea and anemia was diagnosed with multiple PA's. At age 19, she underwent partial resection of a paramediastinal ganglioma; however, part of the tumor remained in situ and was found to be secreting large amounts of dopamine (DA) (11,272 nmol/24 h; normal 650–3270 nmol/24 h). She developed depression, and by age 22 became psychotic and later diagnosed with paranoid schizophrenia while also having elevated urinary DA. Her psychosis was treatment-resistant, and she was treated with clozapine which eventually led to improvement which happened to coincide with normalized catecholamines. The authors did not attribute the schizophrenia to the PA although the evidence could suggest otherwise. Other cases of PC associated with psychosis or neuropsychiatric symptoms support the description of PC as "the great mimic" (Guerrieri et al., 2002; Jain et al., 2011).

3. Discussion

PC and PA have long been associated with symptoms of anxiety and possibly depression but this series of cases indicates psychosis should be added to the psychiatric syndromes that can result from these tumors. The mechanism through which these tumors might cause psychosis remains unknown although certain possibilities exist. First, these tumors are known to secrete elevated levels of catecholamines including DA (Manger and Gifford, 1977), and schizophrenia is reported to have elevated peripheral DA in the range of peripheral DA found in PC (Crowley et al., 1978; Himwich et al., 1967). Although catecholamine release stimulated by stress is a possible explanation of elevated DA in schizophrenia, stress increases norepinephrine release far more than it increases DA (Goldstein and Holmes, 2008). While the association of elevated DA in PC/PA with psychosis that resolves with surgical resection agrees with the general notion that DA is elevated in the striatum in schizophrenia, peripheral DA does not equate to receptor levels of DA nor does it explain how peripheral DA would pass through the blood-brain barrier (BBB) that normally, in the absence of BBB damage, prevents DA and other catecholamines from entering the brain (Kostrzewa, 2007). Perhaps the latter is permitted by BBB damage caused by the extreme hypertension resulting from PC and PA (Johansson and Auer, 1983). The path though the BBB by which peripheral DA might influence mental state, however, remains unclear.

4. Conclusion

As PC and PA are "Great Mimics," clinicians should suspect these diagnoses in cases of autonomic instability or disturbance not only when accompanied by depression or anxiety but also psychosis. These tumors also present an interesting theoretical question as to how they are associated with psychosis. Possibly the psychosis is a paraneoplastic syndrome such as anti-NMDAR-E in which there is a currently unknown receptor antibody secreted by the tumor. Perhaps there is some relationship between peripheral and central DA that is responsible. In either event, further examination of these tumors regarding their role in psychosis may contribute to the understanding of schizophrenia.

Role of funding source
The author received no funding for this work.

Contributors
The author is the only contributor.

Conflicts of interest
The author declares no conflicts of interest.

Acknowledgements
The author has no acknowledgements to declare.

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