Severe Paroxysmal Hypertension (Pseudopheochromocytoma)

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Paroxysmal hypertension always engenders a search for a catecholamine-secreting pheochromocytoma. Yet 98% of people with paroxysmal hypertension do not have this tumor. The cause and management of paroxysmal hypertension remain a mystery, and the subject of remarkably few papers. This review presents an approach to understanding and successfully treating this disorder. Patients experience symptomatic blood pressure surges likely linked to sympathetic nervous system stimulation. A specific personality profile associated with this disorder suggests a psychological basis, attributable to repressed emotion related to prior emotional trauma or a repressive (nonemotional) coping style. Based on this understanding, three forms of intervention, alone or in combination, appear successful: antihypertensive therapy with agents directed at the sympathetically mediated blood pressure elevation (eg, combined α- and β-blockade or central α-agonists such as clonidine); psychopharmacologic interventions including anxiolytic and/or antidepressant agents; and psychological intervention, particularly reassurance and increased psychological awareness. An appropriately selected intervention can reduce or eliminate attacks in most patients.

Introduction

Paroxysmal hypertension is the textbook symptom for a pheochromocytoma, but fewer than 2% of patients with this symptom actually have this tumor [1]. This is not surprising, given the rarity of pheochromocytomas [2]. Typically, diagnostic evaluation reaches a dead end, leaving patients with an unexplained, difficult-to-treat, and often disabling disorder.

The literature provides little guidance regarding clinical management. Although hundreds of papers are available concerning management of patients who have a pheochromocytoma, fewer than two dozen papers deal with the 98% who do not. Doctors and researchers simply do not know how to manage these patients.

This article presents a new understanding of the origin, diagnosis, and successful treatment of otherwise unexplained paroxysmal hypertension, or pseudopheochromocytoma.

Clinical Description

The clinical presentation of pseudopheochromocytoma has been reported [3,4••]. It is more common among women. The frequency of paroxysms ranges from daily to less than one per month, with paroxysms lasting from less than 10 minutes to a few days. Blood pressure levels can exceed 240/140 mm Hg. Hypertensive surges are typically accompanied by physical symptoms such as chest pain, light-headedness, headache, diaphoresis, nausea, palpitations, dyspnea, and weakness. Most patients with severe paroxysmal hypertension are hospitalized at some point and have some degree of impaired functioning [4••].

The fear of recurrent attacks, which typically occur without warning, leads many patients to restrict their activity and even leave their job. Thus, the disorder has a considerable clinical and financial impact.

Clinical Criteria

Many think of pseudopheochromocytoma as a diagnosis by default after a pheochromocytoma has been excluded. Yet its specific characteristics (Table 1) enable the diagnosis to be made with considerable confidence. It is a disorder that is not found in just anyone. The following characteristics define the disorder.

1. *Hypertensive paroxysms characterized by sudden onset*. Patients typically describe paroxysms as having an abrupt onset unassociated with any particular setting or trigger.
2. *Blood pressure elevation is associated with very distressful physical symptoms*. Blood pressure elevation is not asymptomatic. Physical symptoms resemble pheochromocytomas, and include light-headedness, headache, diaphoresis, nausea, chest

Table 1. Clinical features characteristic of pseudopheochromocytoma

1. Hypertensive paroxysms characterized by sudden onset
2. Blood pressure elevation is associated with physical symptoms (eg, headache, flushing, fatigue, dizziness)
3. Episodes are not triggered by emotional distress or panic
4. Biochemical tests have been performed and do not support the diagnosis of pheochromocytoma
5. In nearly all cases, inquiry into psychosocial factors reveals either a history of unusually severe abuse or trauma, or a defensive, very even-keeled personality style

pain, palpitations, flushing, shortness of breath, and weakness [4••,5]. Many patients feel like they are going to die.

3. *Episodes are not triggered by emotional distress or panic*. Unlike panic attacks, hypertensive paroxysms are not heralded by panic. Instead, patients typically insist that paroxysms occur "out of the blue." However, once an episode has begun, the severe physical symptoms typically provoke a fear of dying, a classic symptom of the disorder.
4. *Biochemical tests do not support the diagnosis of a pheochromocytoma*. Because of the similarities between pheochromocytoma and pseudopheochromocytoma and because of the harm done if a curable pheochromocytoma is missed, the possibility of a pheochromocytoma must be considered. This requires biochemical testing of blood or urine levels of catecholamines or catecholamine metabolites, as discussed later [6,7••].
5. *In nearly all cases of severe paroxysmal hypertension, inquiry into psychosocial factors reveals either a history of unusually severe abuse or trauma, or a defensive, very even-keeled personality style*. A distinct psychological profile is characteristic, and is evident in nearly all patients with severe paroxysmal hypertension, as discussed below. This distinct profile provides an important diagnostic clue and enables a confident diagnosis of pseudopheochromocytoma, rather than a diagnosis by default.

Differential Diagnosis

Pheochromocytoma

Excluding pheochromocytoma is the first order of business. If catecholamine studies are abnormal, radiologic studies are needed. Radiologic imaging usually is not indicated when catecholamine studies are normal, particularly if plasma catecholamines were measured during, or urine catecholamines immediately following, an episode.

Many patients have mildly elevated catecholamine levels rather than the extremely high levels usually encountered with pheochromocytoma. Although these high levels deserve attention, they do not merit an unending search for a pheochromocytoma and rarely lead to a diagnosis of this tumor. If plasma norepinephrine is in the range of 1000 to 2000 pg/mL, a clonidine suppression test can be helpful, with a fall in norepinephrine level to the normal range suggesting that a pheochromocytoma is not present [8].

Plasma metanephrine and normetanephrine levels have recently been reported to have high sensitivity and specificity in testing for a pheochromocytoma [7••]. Their plasma half-lives, which are much longer than those of catecholamines, may explain the greater sensitivity. However, clinical experience indicates that mild elevations are common, perhaps related to sympathetic nervous system (SNS) stimulation in patients with paroxysmal hypertension, and should not provoke an endless search for a pheochromocytoma.

It is often difficult for physicians to accept that a patient with paroxysmal hypertension does not have a pheochromocytoma, even if catecholamine levels are normal. Rarely, catecholamine studies can be normal in a patient with a pheochromocytoma, but such cases represent a very uncommon presentation of an uncommon disorder. The likelihood of pseudopheochromocytoma is much greater. The presence of the classic psychological characteristics of pseudopheochromocytoma offers further reassurance of the diagnosis.

Other common conditions

The most common conditions resembling pseudopheochromocytoma, and which need to be differentiated from it, are panic disorder, labile hypertension, and posttraumatic stress disorder.

Panic disorder

Both panic disorder and pseudopheochromocytoma are characterized by sudden episodes of severely distressing physical symptoms (eg, headache, dyspnea, dizziness, weakness, and diaphoresis). The two differ in that attacks are dominated by the emotional manifestation of panic in patients with panic disorder, but not in those with pseudopheochromocytoma. In panic disorder, blood pressure elevation is usually milder (on average 20 mm Hg or less [9]), although some patients experience considerable blood pressure elevation. In contrast, pseudopheochromocytoma is dominated by the autonomic manifestation of a blood pressure surge (40–100 mm Hg or more [4••]), without panic. To a fair extent, the prominence of autonomic versus emotional manifestations is reciprocally related in these two disorders (Fig. 1).

Hypertensive paroxysms can be viewed as the autonomic equivalent of panic attacks, or panic attacks without panic. This perspective led to consideration of antidepressants as treatment.

Labile hypertension

Blood pressure lability is common and should not be misconstrued as pseudopheochromocytoma, unless it has the characteristics defined previously. In some patients, it is asymptomatic, although others experience physical symptoms such as hypertensive or tension headaches. Blood pressure increases can be associated with anxiety or hyperventilation [10]. Unlike patients with pseudopheochromocytoma, most patients with labile essential hypertension readily attribute blood pressure fluctuation to stress and emotional distress.

Posttraumatic stress disorder

Like pseudopheochromocytoma, posttraumatic stress disorder is associated with prior trauma. It is also associated with elevated plasma norepinephrine levels [11]. However, in contrast to pseudopheochromocytoma, severe blood pressure elevation is not characteristic. Also, patients are very aware of the trauma and its impact.

Other medical conditions

Many medical conditions, both common and rare, can also cause paroxysmal hypertension, but seldom provide a diagnosis [4••]. Symptomatic hypertensive encephalopathy can usually be distinguished by a previous history of sustained severe hypertension. Paroxysmal hypertension can be a manifestation of other common and uncommon conditions, such as a brain tumor, various endocrine conditions, or coronary insufficiency, but usually other signs or symptoms typical of those disorders are evident; paroxysmal hypertension is unlikely to be the sole manifestation.

Illicit drugs (eg, cocaine or amphetamines) must be considered, although patients with pseudopheochromocytoma are so symptomatic and frightened that they are unlikely to continue using, or to deny using, these drugs. Ingestion of sympathomimetic agents, monoamine oxidase inhibitors, and tyramine or withdrawal from clonidine should be evident from the history. Baroreceptor failure is extremely unlikely without a predisposing condition, such as prior neck surgery or irradiation [12,13]. In addition, the abnormal blood pressure lability that it causes is continual.

Pseudopheochromocytoma and the SNS

Sudden symptomatic blood pressure surges typical of pseudopheochromocytoma are more likely to be mediated by the SNS, which is responsible for instantaneous changes in blood pressure, than by volume or the renin-angiotensin system. Evidence of increased catecholamine levels during paroxysms support this notion [3]. Kuchel et al. [14] also reported evidence of SNS activation in patients with paroxysmal hypertension, but were unable to identify the cause.

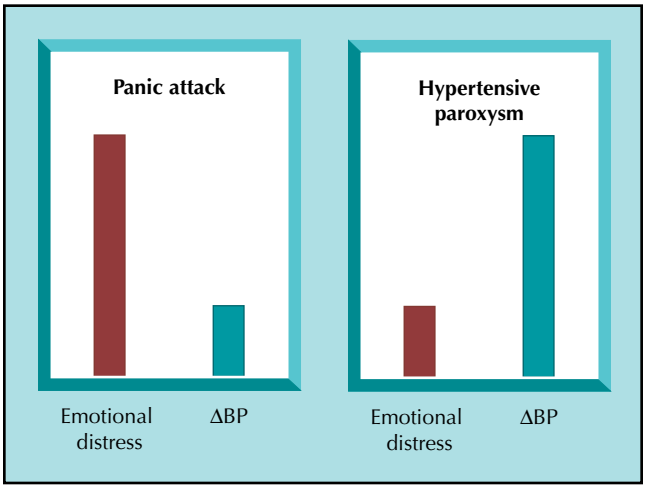

Figure 1. The reciprocal relationship between emotional and autonomic manifestations in pseudopheochromocytoma and in panic disorder. BP—blood pressure.

Hypertensive paroxysms are often characterized by one of two hemodynamic patterns. In some patients, paroxysms are consistently characterized by palpitations and an increased heart rate. In others, the heart rate may be unaffected, or even slowed, during paroxysms.

The increased heart rate and plasma epinephrine level found in some patients with pseudopheochromocytoma resembles the syndrome of hyperdynamic circulatory state described by Frohlich et al. [15], and the primary hyperepinephrinemia described by Streeten et al. [16]. Neither group of investigators identified a cause for the increases in heart rate and epinephrine level.

The previously reported data of two patients illustrate these patterns and reveal an important underlying hormonal difference [3]. In one case, the blood pressure increased to 228/130 mm Hg during a paroxysm, accompanied by cold extremities, reflex bradycardia, and a sixfold increase in plasma norepinephrine, with no increase in epinephrine level. In the other case, the heart rate increased to 96 bpm with a ninefold increase in epinephrine level, and no change in norepinephrine level.

The explanation for these differing hemodynamic patterns can be found in differences in the pattern of SNS stimulation. The SNS is composed of two limbs, the adrenal and the neural. Stimulation of the adrenal limb results in secretion of epinephrine by the adrenal gland, and an increased heart rate and cardiac output. Stimulation of the neural limb results in increased neural release of norepinephrine from sympathetic nerve endings in vascular smooth muscle, and increased peripheral resistance, without an increase in heart rate.

Different stressors can stimulate one limb of the SNS more than the other. For example, anxiety stimulates mainly the adrenal limb. The observed hemodynamic patterns of pseudopheochromocytoma suggest that in

different patients, for reasons that remain unclear, one limb or the other can dominate.

Psychological Roots of Pseudopheochromocytoma

The possibility that pseudopheochromocytoma's origin and its underlying SNS activation are related to psychological factors is largely overlooked. This disregard is understandable because paroxysms are dominated by hemodynamic changes and physical symptoms rather than by emotional distress, panic, or stressful circumstances.

A breakthrough in understanding occurred with the observation that most patients acknowledged a history of unusually severe abuse or trauma, often from as long ago as childhood [3]. Remarkably, most patients claimed they were free of lingering psychological effects, suggesting that they had repressed trauma-related emotions too overwhelming to be borne without adverse psychological consequences. Patients had vivid memories of the trauma without the powerful and painful emotions related to them.

This observation suggested that the psychological origin of pseudopheochromocytoma might involve emotions kept from awareness by defenses such as repression. Contrary to typical psychosomatic approaches, the absence rather than the presence of understandable emotional distress suggests a psychological basis.

Many trauma survivors experience severe emotion early, but eventually manage to repress trauma-related emotion and move forward. However, the repressed emotion has not been obliterated from the unconscious.

It has been widely demonstrated that our emotions affect blood pressure. Because we repress emotions that can be far more overwhelming, it is plausible to suggest their role in otherwise unexplained SNS arousal and paroxysmal blood pressure elevation.

Repression is crucial to emotional health and explains why some victims of severe trauma can survive without apparent adverse psychological effects. They do not report emotional distress, and usually do not even mention old trauma to a physician. The relationship between old trauma and unexplained autonomic surges decades later would never occur to either patient or doctor. Even psychosocially conscious physicians do not ask about previous abuse or trauma, and instead focus on the patient's report of current stress and emotional distress.

Unfortunately, the concept of repressed emotion is foreign to many. Therefore, most physicians and researchers do not consider these concepts and their corollary treatment approaches, even though standard treatments have failed and no other approaches have emerged.

Two patterns of emotional repression

We cannot measure emotions that patients cannot report, but the prominent use of repression can be surmised by paying attention to a patient's life story and personality style. Two patterns of emotional unawareness appear to be associated with pseudopheochromocytoma. The first pattern, seen in about two thirds of patients, consists of a history of severe trauma that most patients claim they have put behind them, strikingly insisting they suffer no lingering effects [4••].

Clinical examples

> A 33-year-old Hispanic man suffered from hypertensive paroxysms with blood pressure elevation as high as 220/140 mm Hg. He reported a childhood history of severe physical abuse by his father. He insisted that he loved his father and bore no anger toward him. Treatment with alprazolam and amitriptyline eliminated hypertensive attacks.

> A 35-year-old foreign-born woman who was a physician experienced debilitating hypertensive paroxysms. She initially reported no prior history of trauma. However, further questioning revealed that, as a college student, she had been detained as a political prisoner for 30 days. She had been blindfolded, her life had been repeatedly threatened, and she had witnessed the death of several friends. After she was freed, she moved on with her life. She insisted there were no emotional aftereffects, had not sought psychotherapy, and had discussed her experiences with no one. Treatment with an antidepressant eliminated the paroxysms.

In trauma survivors, it is important to recognize repression as a successful psychological defense rather than as psychopathology. In handling overwhelming emotion, the alternative to repression is long-term psychological suffering and dysfunction. Many patients with pseudopheochromocytoma have dealt with major trauma through repression, and have led lives marked by considerable achievement. Their resilience can be attributed to their successful use of repression.

The second pattern of emotional unawareness, seen in about one third of patients, is the lifelong tendency to cope unemotionally with the stresses of life [4]. Such patients report never having experienced depression regardless of circumstances. They are doers, not reactors, and tend to be very even-keeled. Because they report little emotional distress, physicians rarely consider their condition as linked to psychological factors.

Clinical examples

> A 66-year-old man suffered from hourlong episodes of blood pressure elevation to 190/110 mm Hg, with diaphoresis and facial reddening. He did not have a history of past trauma, but described himself as very independent, never needing or seeking emo-

tional support, and having a very even temperament (the classic description of a repressor). He reported having shed no tears 7 years earlier when his only son was left permanently paraplegic after a car accident. Treatment with atenolol, terazosin, lorazepam, and desipramine eliminated attacks.

A 52-year-old pampered, well-to-do woman experienced daily hypertensive attacks for 4 months. She insisted she had no stress or distress, and that she was very happy. However, after further discussion, she acknowledged to herself, for the first time, that she was miserable and ashamed because she had no job or purpose and felt useless. Her attacks ceased quickly as she became depressed for the first time in her life. However, the awareness enabled her to initiate changes in her life. Her paroxysms ceased without any medication.

In people with this pattern of not feeling, the absence of emotion is usually a pattern developed in childhood. They are not buffeted by emotions, and the experience of depression or anxiety may be foreign to them.

Approach to Treatment

The treatment of paroxysmal hypertension has been a major dilemma. Diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and adrenergic receptor blockers (ARBs) do not prevent SNS-driven hypertensive surges, nor would they be expected to. The normal blood pressure between episodes precludes an aggressive antihypertensive regimen. Although no controlled treatment trials have been conducted, treatment approaches are needed. Based on the understanding of pseudopheochromocytoma presented in this review, certain approaches—whose validity is suggested by their effectiveness in clinical practice—merit reporting (Table 2). Alone or in combination, they can eliminate paroxysms in most patients and enable them to resume a normal life.

Table 2. Treatment options for paroxysmal hypertension*

1. Antihypertensive drug therapy
a. Acute management of hypertensive paroxysms
i. IV labetalol or nitroprusside
ii. Clonidine
b. Preventive management
i. Combined α- and β-blockade
2. Psychopharmacologic treatment
a. Acute management of hypertensive paroxysms
i. Alprazolam +/– clonidine
b. Preventive management
i. Antidepressant agent (SSRI or tricyclic)
ii. Anxiolytic agent (eg, clonazepam)
3. Psychological interventions
a. Physician intervention
i. Reassurance
ii. Psychological awareness
b. Psychotherapy

*Interventions can be given alone or in combination.
IV—intravenous; SSRI—selective serotonin reuptake inhibitor.

Antihypertensive drug therapy

Acute management of hypertensive paroxysms

The sudden and severe elevation of blood pressure during paroxysms would seem to put patients at risk of an acute cerebrovascular or cardiovascular event. Fortunately, such events seem rare, although more outcome data are needed.

Extreme blood pressure elevation can be treated with rapid-acting intravenous agents, such as labetalol or nitroprusside. With less severe elevation, an oral sympatholytic agent, such as clonidine, can be given either in an emergency department or at home. Oral labetalol may be unreliable because of unpredictable bioavailability due to first-pass hepatic metabolism [17]. Milder paroxysms can be managed in some patients with an anxiolytic agent (see below), given alone or in combination with an antihypertensive agent such as clonidine.

Preventive management

As mentioned earlier, ACEIs, ARBs, and diuretics would not be expected to prevent paroxysms. Also, neither β-blocker monotherapy nor α-blocker monotherapy reduces SNS-mediated blood pressure reactivity [18••]. However, combined α- and β-blockade does, and offers a well-tolerated, logical approach [18••]. Clinical experience indicates this approach can reduce peak blood pressure elevation. Labetalol and carvedilol both provide combined α- and β-blockade, but both suffer from unpredictable bioavailability [17,19]. Therefore, an α-blocker (eg, doxazosin or terazosin) combined with a β-blocker would seem preferable. A central α-agonist such as clonidine is another alternative, although its extended use is limited by side effects, particularly fatigue.

If severe hypertensive paroxysms recur despite treatment, dosage can be guided by the heart rate during paroxysms: if rapid, the β-blocker dose should be increased. If not rapid, it would be logical to instead increase the dose of the α-blocker. When given in combination with a β-blocker, α-blockers such as doxazosin need not be titrated higher than the 2- to 4-mg range for maximal effect [20].

Psychopharmacologic intervention

Acute management of hypertensive paroxysms

A rapid-acting benzodiazepine such as alprazolam can quickly abort attacks in some patients. It can be used

instead of, or in combination with, an antihypertensive agent such as clonidine. The recently released orally disintegrating formulation of alprazolam can reduce response time to a few minutes, allowing administration of a second dose within 10 minutes in nonresponders.

Preventive management

The use of antidepressant and anxiolytic agents to treat pseudopheochromocytoma was suggested by its similarity to panic disorder. Antidepressant agents, including selective serotonin reuptake inhibitors and tricyclic antidepressants (TCAs), appear to prevent recurrence of paroxysms in most patients at dosages recommended for treating panic disorder [3,4]. Improvement is evident within 2 weeks of instituting the effective dose. TCAs are associated with more side effects; however, agents such as desipramine are better tolerated than older TCAs.

Antidepressant agents are effective even in patients who are unwilling to consider psychological factors. In such patients, it is important to emphasize the successful track record of these drugs.

Although an antidepressant can prevent attacks, many patients are reluctant to commit to long-term treatment with a psychotropic agent. A reasonable approach would be to start an antidepressant in patients with extremely severe hypertensive paroxysms (eg, > 220/120 mm Hg) or in those with compromised ability to function. In others, acute management with alprazolam or clonidine, and/or maintenance therapy with combined α- and β-blockade, can be tried first. Delaying initiation of antidepressant treatment also allows for a trial of psychological intervention.

An antidepressant can be given in combination with α- and β-blockade. If paroxysms have ceased, and the patient is otherwise normotensive, the α- and β-blocker can be tapered and stopped, with careful follow-up.

Psychological interventions

Reassurance

Extremely symptomatic hypertensive paroxysms can be terrifying to patients. The fear of dying during an attack can come to dominate their life. A physician's confident reassurance that the disorder can be treated, and that a catastrophic event or death during a paroxysm is very unlikely can help reduce the terror and possibly the number and severity of attacks. Unfortunately, most physicians—lacking understanding of the disorder and experience treating it—cannot provide that reassurance.

Psychological awareness

When the disorder's origin in repressed emotion is explored with patients, some will grasp it at an emotional level. With this awareness, some quickly experience a reduction or elimination of paroxysms without any psychotherapy. Psychotherapy can then be helpful in processing the emotions that arise.

Unfortunately, this shift in awareness usually is not achieved because most patients who are repressing overwhelming emotion related to unspeakable trauma need to continue repressing, and will defend against awareness. They are unlikely to be interested in, or to benefit from, psychotherapy aimed at awareness, and should not be coerced into it. Psychotherapy could even do harm if previously blocked overwhelming emotions are brought to awareness. The dictum that it is always best to deal with the past is not inherently true. Patients who do not have a history of trauma but who have a lifelong tendency to repress are also very resistant to psychotherapy.

The wisest course would be to offer an explanation for the disorder, and reassure the patient that the disorder can be successfully managed and normal life resumed. If the patient comprehends and wishes to pursue psychotherapy, this course can be encouraged. If the patient cannot see the connection of the disorder with trauma or repressed emotion, or prefers not to pursue psychotherapy, psychological discussion and psychotherapy should not be urged.

Obstacles to Successful Treatment

Barriers are encountered with all three treatment approaches. Barriers to treatment with antihypertensive agents include the ineffectiveness of ACEIs, ARBs, and diuretics, and normal blood pressure levels between paroxysms limiting the aggressiveness of antihypertensive therapy. In addition, antihypertensive agents are unlikely to prevent paroxysms.

Barriers to treatment with antidepressants include patients' refusal to try them and, in some cases, multiple drug intolerance that prevents using an effective dose. Many patients refuse to try an antidepressant no matter how severely symptomatic they are because its use implies a psychological cause. Some eventually agree to try one because they are severely symptomatic and no other treatment has helped.

Finally, there are major barriers to psychological intervention. Because pseudopheochromocytoma's manifestations are physical rather than psychological and are not triggered by obvious current stressors, patients and doctors usually do not suspect its emotional basis. Many patients are extremely resistant to the concept that emotions related to events from decades ago might still be affecting them, particularly if they are not experiencing distress. In addition, many patients are unknowingly battling to avoid psychological discussion or awareness. Furthermore, for many patients, the barrier against conscious awareness of overwhelming emotions must be maintained.

Sometimes, merely mentioning the emotional component is so threatening at an unconscious level that the patient might not return for follow-up care. Therefore, the psychological origin must be broached very sensitively,

and it is sometimes best to quickly abandon the topic if a rising resistance is noticed.

Clearly the treatment of pseudopheochromocytoma is a challenge and an art. Fortunately, successful treatment is achievable in most cases, and a normal quality of life can be restored.

Conclusions

Despite all the attention given to pheochromocytoma, 98% of people with paroxysmal hypertension do not have this tumor. Most have pseudopheochromocytoma, whose origin and treatment have received remarkably little attention. Its obscure origin is attributable to its probable link to repressed emotion—a phenomenon essentially unrecognized by patients and even psychologically oriented medical clinicians and researchers. Patients with this disorder seek out physicians, not psychologists; therefore, pseudopheochromocytoma has remained under the radar of psychologists.

The diagnosis of pseudopheochromocytoma is not a diagnosis by default after exclusion of pheochromocytoma and other rare entities. The characteristic psychological background usually allows a confident diagnosis, and greatly reduces concern that a pheochromocytoma or other obscure cause is being missed.

Pharmacologic treatment options include antihypertensive agents, antidepressants, and/or anxiolytic agents. In some patients, understanding the cause of the disorder and reassurance that a catastrophic event is unlikely to occur during an attack can reduce or eliminate the need for pharmacotherapy.

Disclosure

No potential conflict of interest relevant to this article was reported.

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