Suspected Pheochromocytoma in a Patient With Guillain-Barré Syndrome
Fattma Abdel-Salam, Anna Purna Basu, Sally Johnson and Anita M. Devlin

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abstract

Autonomic instability is well recognized in Guillain-Barré syndrome (GBS), particularly in the acute inflammatory demyelinating polyneuropathy subtype. Hypertension occurs in up to two-thirds of children with GBS but is rarely the main presenting feature. We describe a teenager who presented with tachycardia, dizziness, flushing, and significant hypertension as well as ascending limb weakness and sensory disturbance with areflexia. Because the predominant initial concern was hypertension, she was referred to pediatric nephrology and appropriate investigations for hypertension were conducted. Her neurologic findings prompted a neurology referral, and a diagnosis of GBS was made. The investigations for hypertension subsequently revealed increased urinary normetadrenaline levels in a range consistent with pheochromocytoma, prompting the question of dual pathology. Both autonomic symptoms and urinary metadrenaline levels subsided with GBS resolution, and further investigations excluded the diagnosis of pheochromocytoma. Our case highlights that significant dysautonomia can occur in children with GBS, with hypertension being a prominent early feature. Recognition that urinary metadrenalines can increase to levels seen in pheochromocytoma is important in avoiding diagnostic confusion. Pediatrics 2013;131:e955–e958
Autonomic instability is well recognized in Guillain-Barré syndrome (GBS), particularly in the acute inflammatory demyelinating polyneuropathy (AIDP) subtype. However, hypertension is rarely the main presenting feature; indeed, there are only a few reports in children. We describe such a presentation in a teenage girl, in whom investigations for hypertension led to the identification of significantly increased urine normetadrenaline levels, leading to concerns regarding possible dual pathology with both GBS and pheochromocytoma.

**PATIENT PRESENTATION**

A previously healthy 14-year-old girl was referred to the pediatric nephrologists at our Children’s Hospital for management of significant hypertension. She had developed neck and back pain after falling down stairs several days previously. Imaging had excluded spinal injury. However, she was noted to be persistently hypertensive with a blood pressure (BP) of 160 to 180/115 mm Hg (99.9th percentile for height, age, and gender), sustained tachycardia of ~120 beats per minute, and diminished circadian variability. She had recently been noted to be normotensive by her general practitioner. She also complained of dizziness, flushing episodes, excessive sweating, headaches, and gradual development of leg weakness and distal sensory disturbance.

On examination she was afebrile. Heart sounds were normal, and peripheral pulses were palpable. A respiratory and gastrointestinal system examination was unremarkable. She was able to walk several steps with support. Her tone was normal although both legs were weak (Medical Research Council [MRC] grade 4 distally) and areflexic with downgoing plantar responses and distal dysesthesia. In the upper limbs, mild weakness and absent biceps jerks were noted.

At this stage, the nephrologist requested investigations for hypertension according to the local protocol. Electrocardiogram and echocardiogram were performed that day and were normal, as were full blood count, urea and electrolytes, bone profile, and liver function tests. In view of her initial fall, neck injury, and evolving neurologic signs the neurosurgical team were also alerted. Once again, spinal injury was excluded as a cause but given her weakness, areflexia, and sensory symptoms, GBS was suggested as a likely explanation and she was referred to the neurology team. Nerve conduction studies performed 10 days after the initial symptoms showed patchy reduction in motor conduction velocity in the lower limbs, with temporal dispersion and conduction block. F-wave latencies were prolonged or absent (left tibial F-wave latency 70.8 ms). Cerebrospinal fluid examination revealed an increased protein level of 2.65 g/L with normal glucose, but 36 white cells and 4 red cells per cubic millimeter. A porphyria screen and test for antiganglioside antibodies were performed and subsequently found to be negative.

A diagnosis of the AIDP subtype of GBS was made, with hypertension presumed to be secondary to autonomic dysfunction. The patient received standard intravenous immunoglobulin therapy. Spirometry measurements remained stable. The flushing episodes resolved within days, but the patient remained significantly tachycardic and hypertensive. Fifteen days into the acute illness (a week after her admission), the full results of the hypertension screen, including urinary metadrenaline levels, became available. Plasma renin activity and aldosterone, immunoglobulins, serum electrophoresis, complement (C3 and C4), and an autoantibody screen were normal. However, the 24-hour urine normetadrenaline level was significantly elevated at 4.2 μmol/24 hours (reference range: 0.3–1.5 μmol/24 hours), and the urine metadrenaline level was elevated at 1.5 μmol/24 hours (reference range: 0.2–1.2 μmol/24 hours), leading to consideration of a diagnosis of pheochromocytoma.

At this stage, endocrinology review was requested. The abdominal computed tomography (performed at presentation to exclude injury) was reviewed, and adrenal glands were normal. Plasma metadrenalines were measured and shown to be normal, although the urinary metadrenaline level remained elevated at 4.7 μmol/24 hours. These findings excluded pheochromocytoma as the cause of the elevated metadrenaline levels.

The patient remained significantly tachycardic and hypertensive, with gradual resolution over several weeks (Fig 1). She received regular physiotherapy input and was able to walk independently with minor distal weakness on discharge 1 month later. By this time, urinary metadrenaline levels remained only marginally elevated, and the urinary metadrenaline level was in the normal range (Fig 1). On review 3 months later, lower limb examination, gait, and BP were normal.

**DISCUSSION**

Autonomic dysfunction in GBS is well recognized, particularly in the AIDP subtype, and can have life-threatening consequences. In a review of children with GBS, 20 of 30 had elevated BP with significant correlation between hypertension and disease severity, length of hospital stay, and higher cerebrospinal fluid protein level. In this study, the onset of BP elevation occurred on average of 4.9 days after the onset of neurologic symptoms (range: 1–14 days), and BP elevation was present for 9.9 of the first 14 hospital days (range: 3–14 days).

It is unusual, however, for hypertension to be the main presenting feature of
GBS, although this has been described, often in association with other presenting features. Smith et al reported 2 children with GBS aged 5 and 3 years who presented with unilateral facial nerve palsy and hypertension. The first developed lower limb pain and weakness with hyporeflexia over the next 48 hours, leading to recognition of the GBS diagnosis. Lacroix et al described a 9-year-old child who presented with respiratory distress as the predominant feature but also with weakness, limb pain, and hypertension. A further report by Singer and Back cited a child who presented with bilateral limb pain and “postural guarding,” again with hypertension as an initial manifestation. There are also reports of GBS in the pediatric population who present initially with significant hypertension associated with status epilepticus and hypertensive encephalopathy. In the adult literature there is a report of a patient with GBS who presented initially to the coronary care unit with chest pain and hypertension. Another report described an 82-year-old woman who presented with back pain and hypertension for whom aortic aneurysm or dissection were the initial working diagnoses. The further interesting twist in our patient’s case is that investigations for the cause of hypertension led to identification of elevated urinary metadrenaline levels and consideration of a diagnosis of pheochromocytoma in addition to that of GBS. The cooccurrence of both pheochromocytoma and GBS in 1 patient, although not impossible, would have been a very unlikely occurrence. The incidence of GBS is ~1 per 100 000 patient-years, and the incidence of pheochromocytoma is just slightly less than this. The sustained hypertension, tachycardia, sweating, and dizzy spells seen in our patient are all also features of pheochromocytoma, although pallor is seen more commonly than flushing due to high circulating norepinephrine levels. Pheochromocytoma is a catecholamine-producing tumor arising from the chromaffin cells of the sympathetic nervous system. It accounts for 1% of cases of childhood hypertension. Severe, sustained hypertension was the most consistent sign occurring in 93% of a group younger than 20 years who presented with pheochromocytoma. Although treatable, this is a potentially fatal condition and sensitive tests are therefore used for screening, leading to frequent false-positive results. False-positive results have also been reported secondary to medication use. The measurement of urinary or fractionated plasma metadrenaline levels (normetadrenaline and metadrenaline) has been shown to have better diagnostic sensitivity for pheochromocytoma than measurement of the parent catecholamines. A normal fractionated plasma metadrenaline level virtually excludes a diagnosis of a pheochromocytoma, which, in combination with normal adrenal imaging, ruled out the diagnosis of pheochromocytoma in our patient. The finding of elevated urinary metadrenaline levels is, however, in line with the published literature on GBS. Specifically, Ahmad et al found that plasma and urine catecholamine levels were elevated only in patients with GBS who had autonomic instability. The question of why increased catecholamine levels are seen in such patients remains incompletely answered. Increased sympathetic nervous system activity has previously been observed in the acute stage in GBS, which could lead to increased release of catecholamines from the adrenal gland. It seems, however, counterintuitive that overactivity within the sympathetic nervous system could be due to a demyelinating neuropathy, particularly because the postganglionic sympathetic nervous system fibers are myelinated. Therefore, damage to the afferent limb of baroreceptor reflexes, causing reduced inhibition of vasmotor centers, has been suggested as the cause of the increased sympathetic outflow. However, autonomic

FIGURE 1
Changes in cardiovascular parameters over time and relationship to urinary normetadrenaline levels, treatment, and disease nadir: Vertical lines represent systolic (top) and diastolic (bottom) BP measurements (mm Hg), respectively. Triangles represent heart rate (HR; beats per minute). The + signs represent urinary normetadrenaline values (µmol/24 h), plotted by using a secondary axis. The term “disease nadir” refers to the point at which neurologic signs and symptoms were at their most severe. IVIG refers to intravenous immunoglobulin treatment.

Severe, sustained hypertension was the most consistent sign occurring in 93% of a group younger than 20 years who presented with pheochromocytoma. Although treatable, this is a potentially fatal condition and sensitive tests are therefore used for screening, leading to frequent false-positive results. False-positive results have also been reported secondary to medication use. The measurement of urinary or fractionated plasma metadrenaline levels (normetadrenaline and metadrenaline) has been shown to have better diagnostic sensitivity for pheochromocytoma than measurement of the parent catecholamines. A normal fractionated plasma metadrenaline level virtually excludes a diagnosis of a pheochromocytoma, which, in combination with normal adrenal imaging, ruled out the diagnosis of pheochromocytoma in our patient. The finding of elevated urinary metadrenaline levels is, however, in line with the published literature on GBS. Specifically, Ahmad et al found that plasma and urine catecholamine levels were elevated only in patients with GBS who had autonomic instability. The question of why increased catecholamine levels are seen in such patients remains incompletely answered. Increased sympathetic nervous system activity has previously been observed in the acute stage in GBS, which could lead to increased release of catecholamines from the adrenal gland. It seems, however, counterintuitive that overactivity within the sympathetic nervous system could be due to a demyelinating neuropathy, particularly because the postganglionic sympathetic nervous system fibers are myelinated. Therefore, damage to the afferent limb of baroreceptor reflexes, causing reduced inhibition of vasmotor centers, has been suggested as the cause of the increased sympathetic outflow. However, autonomic
dysfunction in GBS is still incompletely explained.

This case is important in highlighting the degree of dysautonomia that can occur with GBS. Specifically, we alert clinicians to the fact that hypertension can be a predominant early feature and can be accompanied by tachycardia, flushing, sweating, dizziness, and elevated urinary metadrenalines to levels seen in pheochromocytoma. The recognition of this phenomenon is important in avoiding diagnostic confusion and unnecessary investigations. Plasma metadrenaline levels are the most appropriate subsequent test if urinary metadrenaline levels are elevated. If plasma metadrenaline levels are normal, and the hypertension and elevated urinary metadrenaline levels resolve as the GBS improves, further investigations for pheochromocytoma are not needed.

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