Pharyngeal-cervical-brachial variant of Guillain-Barré syndrome in a patient with thalassemia intermedia

Keivan Basiri, MD, *Farzad Fatehi,* MD, *Fatemeh Derakhshan,* MD.

ABSTRACT

نستعرض في هذا التقرير المثال الأول لتغير متلازمة جوليان–باري لدى مريضة تعاني من ثلاسيميا بيتا، وزيادة حمل عنصر الحديد، والتي أجريت لها في السابق عملية نقل الدم قبل ظهور الأعراض. تبلغ المريضة 50 عاما، وهي سيدة فارسية تعاني من الثلاسيميا الوسطية والتي تمت معالجتها بالتزويد بخلايا الدم نتيجة لنقص مستوى الهيموجلوبين. بعد 10 أيام من عملية نقل الدم، تعرضت المريضة لتنمل في الذراع واسترخاء في الجانب الأيسر، تلاها عسر الكلام، البلع، واسترخاء في الجانبين. أظهر التشخيص الكهربائي في اليوم الثاني عشر انخفاض في تكرار الموجات F في كلا الطرفين العلويين، وانخفاض الرجفان +1 في عضلات الوجه. كانت نتيجة تخطيط العضلات الكهربائي ودراسة توصيل العصب في الأطراف طبيعية. بعد اختتام الأسباب الأخرى وفقاً للتشخيص الكهربائي، تم اعتبار الحالة بمتلازمة جوليان– باري لمتغيرات البلعوم والعنق والعضد، وتم البدء في استبدال البلازما. عقب الاستبدال، طرأ على المريضة تحسن سريري ملحوظ. نستنتج من هذه التقرير، أن زيادة حمل عنصر الحديد وانتقال العدوى المحتملة من مشتقات الدم في تطور المتلازمة.

Here, we present the first instance of Guillain-Barré syndrome variant in a patient with beta thalassemia and iron overload who had a history of transfusion before the onset of symptoms. Our patient was a 50-year-old Persian woman with history of intermediate thalassemia who had been treated with pack cells because of low hemoglobin level. Ten days after transfusion, she developed numbness of arms, left sided ptosis, and afterwards dysarthria, dysphagia, and bilateral ptosis. Electrodiagnosis on day 12 revealed reduced repetition of f-waves in the upper limbs and reduced recruitment with 1+ fibrillation in facial muscles. Electromyography and nerve conduction velocities in the limbs were normal. After excluding other causes and according to electrodiagnosis, the pharyngeal-cervical-brachial variant of Guillain-Barré syndrome was considered and plasma exchange began. Following exchanges, significant clinical improvement was attained. Iron overload and possible transmission of infections from blood products might have contributed in the development of syndrome.

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From the Departments of Neurology (Basiri, Fatehi), and Isfahan Neurosciences Research Center (Basiri, Fatehi, Derakhshan), and Medical Education Research Center (Fatehi), Isfahan University of Medical Science, Isfahan, Iran.

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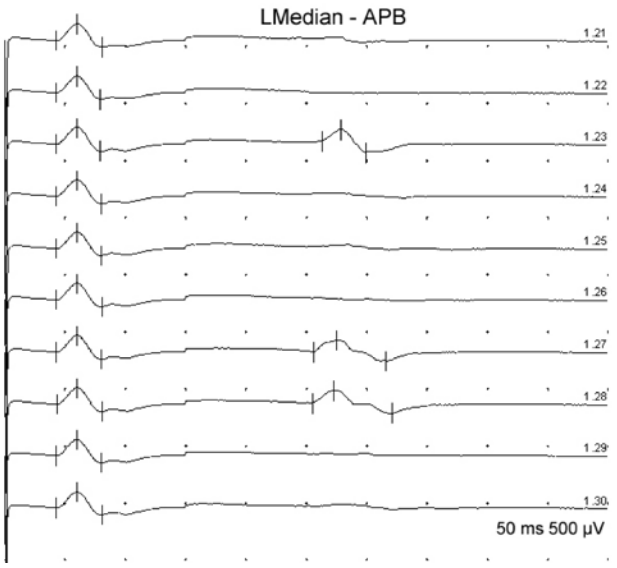
Address correspondence and reprint request to: Dr. Keivan Basiri, Assistant Professor of Neurology, Neurology Department, Alzahra Hospital, Sofeh Street 81744, Isfahan University of Medical Sciences, Isfahan, Iran. Tel. +98 (913) 3290713. E-mail: basiri@med.mui.ac.ir

Guillain–Barré syndrome (GBS) is clinically characterized by an acute onset of generalized and symmetrical muscle weakness and areflexia from peripheral nerve involvement.[1] Diagnostic criteria for GBS do not encompass the full clinical spectrum of this disorder, so that the diagnosis is based on consistent clinical, laboratory, and neurophysiologic findings, and exclusion of other conditions with parallel presentations.[1] There are a number of variant forms of GBS, which are classified by their clinical manifestations and variable involvement of motor and sensory axons of peripheral nerves and the autonomic nervous system. However, in GBS-variants some patients have unusual distribution of muscle involvement. Here, we present a case of the pharyngeal-cervical-brachial (PCB) variant of Guillain-Barré syndrome in a patient with beta thalassemia and iron overload who had a history of transfusion before the onset of symptoms. This case demonstrates difficulty in diagnosis of some variants of GBS, absence of clear-cut electrodiagnostic (EDX) findings in the early stages of disease, and unusual EDX findings on subsequent examination.

Case Report. Our patient was a 50-year-old Persian woman with a history of intermediate thalassemia who had been treated with 2 units of pack cells because of low hemoglobin on lab exams. Ten days after transfusion, she developed numbness of arms, pain in right arm, left sided ptosis, and bilateral blurred vision. After 4 days the signs progressed to dysarthria, dysphagia, and bilateral

Figure 1 - The only finding on the first nerve conduction study was reduced repetition of F-waves in the upper extremities.



ptosis. Because of probable vertebrobasilar insufficiency, she was treated with heparin and warfarin in a general hospital. She was also evaluated for rhombencephalitis and received empirical therapy of ampicillin for a few days. On day 5, she was referred to our tertiary University hospital. On admission, she was conscious, suffered from nasal speech, and dysphagia. Neurological examination revealed mild bilateral facial palsy, bilateral ptosis, and limitation of right horizontal gaze. Pupils were midsize and reactive. Strength of the neck flexors and extensors was normal. Shoulder abduction, elbow flexion, and extension, and external rotation of the arm were 4/5. Wrist extension and movements of the hand intrinsic muscles were 5/5 bilaterally. Strength in the legs was normal apart from trace weakness of the hip flexors. Muscle tone was normal throughout. The deep tendon reflexes were normal in arms and legs. The plantar responses were flexor, and sensation was intact. There was no ataxia or tremor. Her gait was normal. The abdominal reflexes were present, and sphincter function was normal. The systemic examination revealed mild splenomegaly because of mild hemolysis. Her complete blood count (CBC) lab data showed thrombocythemia (which was treated by hydroxy-urea) and low hemoglobin (with normal reticulocyte count and hypo-chromic red cells and target cells in peripheral blood smear). A high level of ferritin (800 ng/ml, normal range [NR] = 40-200 ng/ml) demonstrated iron overload. Initial cervical and brain MRI was reported as normal. Considering myasthenia gravis crisis, she underwent plasma exchange 25 cc/kg on alternate days. The EDX on day 12 revealed reduced repetition of f-waves (**Figure 1**) in the upper limbs, and reduced recruitment with 1+ fibrillation in facial muscles. Routine electromyography (EMG) and nerve conduction studies (NCS) in the limbs were normal (**Table 1**). Cerebrospinal fluid analysis showed 3400 RBC/mm^3 (because of traumatization), 5 WBC/mm^3, 111 mg/dl protein (NR = <45 mg/dl), and 113 mg/dL glucose (NR = >40% of blood glucose), (blood sugar = 199 mg/dL). The CSF analysis for Borrelia antibody and angiotensin converting enzyme (ACE) was unrevealing. The herpes simplex virus polymerase chain reaction exam, CSF, and blood culture were all negative. Repetitive nerve stimulation test was normal. Concurrently, acetylcholine receptor antibody (AChR Ab) was reported negative (AChR Ab=0.1, <0.25 considered negative). Based on the above results the PCB variant of GBS was considered, and plasma exchange continued (50 cc/kg on alternate days). On day 14, she developed decreased muscle power (2/5 in proximal upper limbs, and 3/5 in proximal lower limbs, and normal in distal), generalized hyporeflexia (the deep tendon reflexes were absent on both arms and 1+ on the legs), respiratory distress, and bulbar palsy requiring intubation and mechanical ventilation. After 5 sessions of plasma exchanges, due to lack of response, intravenous

Table 1 - Nerve conduction studies on day 12.

Nerves studied	DML (ms)	DSL (ms)	SNAP Amplitude (µv)	CMAP Amplitude (mv)	Motor Velocity (m/s)	Sensory Velocity (m/s)	Mean F latency (ms)
R Median	3.05	3.30	17.7	10.9	59.7	58.3	25.17
L Ulnar	2.05	2.65	33.1	7.0	56.0	52.4	24.91
R Tibial	3.60			3.5	44.0		48.29
L Peroneal	2.65			3.8	47.7		47.91
R Sural		4.05	10.0			41.8	

DML - Distal motor latency, DSL - Distal sensory latency, SNAP - Sensory nerve action potential, CMAP - Compound muscle action potential, R - right, L - left

Table 2 - Nerve conduction studies on day 36.

Nerves studied	DML (ms)	DSL (ms)	SNAP Amplitude (μv)	CMAP Amplitude (mv)	Motor Velocity (m/s)	Sensory Velocity (m/s)	Mean F latency (ms)
R Median	3.60	3.25	24.0	3.4*	50.5	58.3	27.07
L Ulnar	2.30	3.10	28.8	2.3†	53.7	55.0	26.38
R Tibial	5.05			3.0	40.0		55.17
L Peroneal	4.54			2.1	41.6		53.50
R Sural		4.05	14.0			43.1	

DML - distal motor latency, DSL - distal sensory latency, SNAP - sensory nerve action potential, CMAP - compound muscle action potential, R - right, L - left, *normal range = ≥4, †normal range = ≥6,

immunoglobulin 0.4 g/kg/day was started. Mechanical ventilation continued for 2 weeks and after 20 days, tracheostomy was performed. The EDX was repeated on day 36 (**Table 2**). Nerve conduction study revealed reduced compound muscle action potential (CMAP) amplitude with preserved motor nerve conduction velocity (NCV), reduced repetition of F-waves, and normal sensory nerve action potential amplitude and sensory NCV in all 4 limbs. On EMG, reduced recruitment with profound fibrillation and positive sharp waves were detected in all tested muscles in the distribution of all roots in bulbar, cervical, thoracic, and lumbosacral myotomes (facial, limb, and paraspinal muscles). Second brain and cervical MRI were normal, and second CSF analysis (performed 38 days after admission) showed 0 RBC/mm^3, 0 WBC/mm^3, and 28 mg/dl protein. The CSF analysis for Borrelia antibody and ACE was reported normal again. Her movements improved gradually; on day 50, her ptosis and dysphagia resolved completely, but tracheostomy could not be closed due to persistent weakness of respiratory muscles. Generalized hyporeflexia persisted. The muscle power of proximal upper and lower limbs was 4/5, and distal limbs were normal as well. At this stage, she resumed the ability to walk. Respiratory rehabilitation began and after 5 months the tracheostomy was closed successfully.

Discussion. A number of variant forms of GBS are identified on the basis of atypical clinical presentation and neurophysiologic findings.[2,3] The Miller Fisher syndrome, PCB, and polyneuritis cranialis variants of GBS have prominent cranial nerve involvement. These limited regional variants account for approximately 7-13% of adult cases of GBS.[4] Ropper et al,[2] first reported 3 patients with oropharyngeal, neck, and shoulder muscle weakness, and categorized the condition as a variant of GBS, the PCB variant.[2] Recently, Dogonadze et al's[5] study showed the role of free iron as an oxidative stress in viral polyneuropathy pathogenesis. Our patient suffered from iron overload due to intermittent transfusion, but she had not received any iron chelating therapy to date. Her last transfusion was 10 days before onset of disease, which is the usual time for occurrence of GBS predisposing factors. Although there is not sufficient evidence of a possible role of blood transfusion in the onset of the GBS, Merelli et al[6] also reported a case that developed acute polyradiculoneuritis after a series of blood transfusions. She developed acute polyradiculoneuritis 7 days after a series of 4 blood transfusions. In their case, absence of all factors that usually precede the onset of the disease suggested a possible role of blood transfusion in the onset of the GBS. Furthermore, GBS development after transfusion might have been a result of probable occult infections of blood products; although in Iran blood products are evaluated regularly and carefully. Therefore, the role of iron overload in inflammatory damage of the nervous system, besides suspected transmission of infections from blood products might have contributed to the pathogenesis of GBS development. Another report showed GBS in a patient with sickle cell anemia (another hemoglobinopathy), who had a mild clinical course of the disease before developing the symptoms.[7] The symptoms included ascending paralysis, areflexia, sensory disturbance, and bulbar affectation; contrarily our patient's symptoms started from the lower limbs accompanied by further involvement of bulbar nerves.

Given their atypical presentation, the variants of GBS may not be identified as such until alternative diagnoses are excluded.[8] In our patient, vertebrobasilar infarction, and rhombencephalitis was considered due to her initial presentation. The early diagnosis of rhombencephalitis was based on the clinical features, before CSF analysis and the brain MRI. Myasthenia gravis was also contemplated, given the severity of her bulbar weakness, but was excluded on clinical grounds and by the neurophysiologic findings. The clinical course, raised CSF protein with normal WBS and glucose on the first CSF examination (second week), return of CSF protein

into the normal range on the second CSF analysis (day 38), electrophysiological studies, and exclusion of other probable etiologies confirmed the diagnosis of GBS.

The role of immune-modulating therapies for the regional forms of GBS is not clear, but treatment with immunoglobulin or plasma exchange seems warranted in patients with severe weakness, loss of ambulation, or significant respiratory compromise. Immunoglobulin is probably the agent of choice in patients with antibody-mediated GBS.[9] Isolated absence of f-wave has been reported by Kuwabara et al[10] in the first electrophysiological studies of 19% of GBS patients.[10] In our case all f-waves were obtainable on the first EDX study on day 12, and the isolated finding on NCS was reduced repetition of F-waves in the upper extremities. On the second study on day 36, completely normal sensory NCS with reduced CMAP amplitude suggests the conceivable acute motor axonal neuropathy (AMAN) variant of GBS, but normal motor NCV and reduced recruitment with profound fibrillation and positive sharp waves on EMG of paraspinal and facial muscles makes this case distinct from the AMAN variant and localizes the lesion at the level of the roots (diffuse polyradiculopathy).

In conclusion, GBS should always be considered in patients presenting with multiple cranial nerve palsies, and transfusion may be considered as one of the possible predisposing factors in developing GBS. Also, we should remember that GBS could present with EDX findings of polyradiculopathy without peripheral nerve involvement.

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