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A Possible Guillain-Barre Syndrome Associated with Diabetic Ketoacidosis: A Case Report and Literature Review

Diyabetik Ketoasidozla İlişkili Olası Bir Guillain-Barré Sendromu: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract
Guillain-Barre Syndrome (GBS) is an acute inflammatory polyradiculoneuropathy. Diabetic ketoacidosis (DKA) is a serious, life-threatening complication of Type 1 diabetes mellitus (DM). In the pathogenesis of Guillain-Barre Syndrome and DKA, autoimmunity plays a role. A thirty-five year old male patient, who had been followed up in endocrinology service with a diagnosis of diabetic ketoacidosis (DKA), complained of weakness in the arms and legs on the seventh day of hospitalization. The patient had no diseases except for diabetes mellitus type 1. The patient was diagnosed with Guillain Barre Syndrome (GBS) on the basis of neurological examination, cerebrospinal fluid results and electrophysiological findings. Clinical improvement was observed as a result of intravenous immunoglobulin therapy. Diabetic ketoacidosis induced GBS was considered for the patient. There is no study that points to diabetes mellitus or DKA as risk factors for GBS. Case reports of Guillain Barre Syndrome associated with diabetic ketoacidosis are rare in the literature.
Keywords: Diabetic Ketoacidosis; Guillain Barre Syndrome; Treatment.

Öz
Guillain Barre Sendromu (GBS) akut inflamatuvar bir poliradikülonöropatidir. Diyabetik ketoasidozis (DKA) ciddi, hayatı tehdit edici tip 1 diyabetes mellitusun (DM) komplikasyonudur. Guillain Barre sendromu ve diyabetik ketoasidozus patogenezinde otoimmunite rol alır. Otuzbeş yaşında erkek hasta diyabetik ketoasidoz tanısıyla endokrinoloji servisinde izlenmekte iken yatışının 7. gününde kol ve bacaklarında güçsüzlük yakınması gelişti. Tip 1 diyabetes mellitus dışında bilinen bir hastalığı yoktu. Nörolojik muayene, beyin omurilik sıvısı ve elektrofizyolojik bulgular ile Guillain-Barré Sendromu tanısı konuldu. İntravenöz immunglobulin tedavisi ile klinikte düzelme izlendi. Olgumuz da DKA'un tetiklediği GBS düşünülmüştür. Guillain Barre sendromu risk faktörü olarak diyabetes mellitus veya DKA'u işaret eden bir çalışma yoktur. Literatürde çok az sayıda olgumuza benzer vaka sunumları vardır.
Anahtar Kelimeler: Diyabetik Ketoasidoz; Guillain Barre Sendromu; Tedavi.

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INTRODUCTION

Guillain-Barre Syndrome (GBS) is an acute inflammatory polyradiculoneuropathy usually characterised by progressive, ascending, symmetrical power loss and areflexia (1). Clinical signs usually occur 2-4 weeks after non-specific infection (2). Diabetic ketoacidosis (DKA) is a serious, life-threatening complication of diabetes mellitus (DM) that is especially common in children with Type 1 diabetes. It manifests itself due to drastic reduction of insulin and increased secretion of anti-insulin hormones like glucagon, adrenaline, cortisol, and growth hormone. Besides, intercurrent infections, emotional stress, and other similar factors lead to increased insulin requirements (3, 4). In the pathogenesis of Guillain-Barre Syndrome and DKA, autoimmunity plays a role. This paper presents the case of a patient who developed GBS during diabetic ketoacidosis treatment.

CASE REPORT

A thirty-five-year-old male patient was admitted to the emergency room with complaints of continued weakness, vomiting, joint pain, and intermittent fever that had been going on for five days. It was learnt that the patient had started an antibiotic treatment at an outside facility with no change in the symptoms. The laboratory examination results were was follows: serum glucose 394 mg/dL; blood urea nitrogen: 17 mg/dL; creatinine 0.9 mg/dL; alanine aminotransferase 35 IU/L; aspartate aminotransferase 47 IU/L; sodium 135 mmol/L; potassium 3.9 mmol/L; white blood cell count 13,000/mm3; and positive (+++) glucose and ketone in complete urinalysis. The patient was taken to the endocrinology service for monitoring with a diagnosis of diabetic ketoacidosis. On the 7the day, he developed weakness in the distal of his lower extremity which spread to the upper limbs. within 2-3 days. The patient did not have any known diseases except for Type 1 DM which was diagnosed 25 years ago. We learnt that the patient had been using insulin for diabetes mellitus for the last 10 years. The medical history of the patient also revealed that he had neuropathic pain prior to hospitalisation. The patient did not have recent upper or lower respiratory tract infection or diarrhoea. Neurological examination revealed a muscle strength of 3/5 in the lower extremities and a muscle strength of 4/5 in the upper extremities. There was no facial diplegia. Deep tendon reflexes were lost and the patient had glove and stocking hypesthesia (with no revealing sense defects). The protein level in the cerebrospinal fluid (CSF) was 141 mg/dL with no pleocytosis. There was no electrolyte imbalance in the blood examination; the haemoglobin A1C level (10.8%) was high. The laboratory tests requested for the diagnosis of potential infections and CSF results were normal. With a treatment targeted at diabetic ketoacidosis, the blood sugar levels of the patient were brought down to normal levels within the first three days. The electroneuromyography (ENMG) on the sixth day of the onset of clinical picture showed mixed type polyneuropathic involvement that basically affected sensory nerves (there was no observed transmission blocks; there was delayed motor distal latency in the upper extremity; conduction velocity was slow; and F responses were delayed). The needle EMG revealed increase win motor unit potential amplitude; the frequency was diluted with polyphase (Table 1).

Having evaluated the clinical, CSF and electrophysiological findings all together, we considered the possibility of GBS after the differential diagnosis. The treatment consisted of intravenous immunoglobulin (IVIG) (0.4 g/kg/day) administration for 5 days. The examination on the 20th showed a muscle strength of 4+/5 in the upper and lower extremities. With improved clinical status in the follow-ups, the patient has been followed by neurology and endocrinology clinics for 12 months.

Table 1. Nerve conduction studies (Day 6)

	Stimulated area	Amplitude Motor:mV, Sensorial: μV	Latency ms	Speed m/s	F frequency ms
Median (R)	Wrist	NR (>20)	NR (<3,4)	NR (>50)	
Ulnar (R)	Wrist	NR (>18)	NR (<3,0)	NR (>50)	
Sural (R)	Calf	NR (>5)	NR (<4,5)	NR (>40)	
Median (R)	Wrist	9,4 (>5)	5,80 (<4,1)	35 (>50)	
	Elbow	7,1	12,90		
Ulnar (R)	Wrist	9,9 (>7)	4,85 (<3,1)	31 (>50)	36 (<32)
	Sub-ulnar	8,2	11,1		
Peroneal (R)	Wrist	1,2 (>3)	7,55 (<5,1)	33 (>40)	59 (<50)
	Lower knee	0,9	13,2		
Tibial (R)	Wrist	2,3 (>6)	9,40 (<5,5)	29 (>40)	68 (<51)
	Knee	1,8	17,5		
Median (L)	Wrist	NR (>20)	NR (<3,4)	NR (>50)	
Ulnar (L)	Wrist	NR (>18)	NR (<3,0)	NR (>50)	
Sural (L)	Calf	NR (>5)	NR (<4,5)	NR (>40)	
Median (L)	Wrist	8,5 (>5)	6,10 (<4,1)	37 (>50)	
	Elbow	8,1	14,1		
Ulnar (L)	Wrist	9,5 (>7)	5,15 (<3,1)	38 (>50)	37 (<32)
	Sub-ulnar	7,7	9,8		
Peroneal (L)	Wrist	2,2 (>3)	6,40 (<5,1)	35 (>40)	57 (<50)
	Lower knee	1,4	11,3		
Tibial (L)	Wrist	1,9 (>6)	9,40 (<5,5)	34 (>40)	67 (<51)
	Knee	1,3	18,8		

APB: Abductor Pollisis Brevis; **ADM:** Abductor Digiti Minimi; **EDB:** Extensor Digitorum Brevis; **AH:** Abductor Hallusis; **R:** Right; **L:** Left; **NR:** No response.

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DISCUSSION

Diabetic ketoacidosis is the most important cause of morbidity and mortality in type 1 diabetes. In DKA patients, blood glucose is around 200 mg/dL and serum osmolality is over 320 mmol/l while blood pH is acidic. Insulin deficiency results in unavailability of glucose which leads to hyperglycaemia and hyperosmolarity; these pictures further lead to essential dehydration and electrolyte loss (3, 4). Guillain-Barré syndrome is an autoimmune disease that develops as a result of production of antibodies by peripheral nerves against antigenic proteins due to T cell activation. Antibodies target myelin though, in some cases, axons may also be the target of immune-mediated damage. Antibody production is triggered by infectious agents, surgical procedures, birth, and immunization (5). Although infections cause the onset of GBS in 3/4 of cases, other rare causes in the literature are malignancy (such as Hodgkin's lymphoma), systemic lupus erythematosus, sepsis, multiple organ failure, disseminated intravascular coagulation (DIC), and other systemic diseases (6-10). A small number of acute polyneuropathy cases have also been reported as a complication of diabetic ketoacidosis (11).

Our patient, who had Type 1 DM, complained of neuropathic pain before hospitalisation. The intravenous immunoglobulin treatment fixed his complaints of weakness though he still had ongoing neuropathic pain. We thought that neuropathic pain and glove and stocking hypesthesia could be induced by diabetes.

Although there is no study that points to diabetes mellitus or DKA as risk factors for GBS, there are studies reporting DKA-induced GBS (12-14) as it was the case in our patient.

In recent years, it has been reported that GBS may follow a course similar to those of critical illnesses (such as DIC and sepsis). The mechanism of GBS developing in patients with diabetic ketoacidosis is not yet fully known. Among the hypotheses, there are the T-cell response developing against the antigens on nerve surface and release of inflammatory mediators leading to humoral immune response due to complement activation on the surface of nerves. Although the most common cause of GBS is infectious causes, critical illness such as DKA may also result in initiation of immune responses. Despite the reports suggesting this atypical course of GBS, there is need to investigate its pathophysiology and need for more extensive studies on more patients.

The fact that there are no studies in the literature showing any antibodies that can be related to both GBS and diabetes at the same time and that some cases lack the infection-related causes weakens the hypothesis of autoimmunity pathogenesis (12, 14). The presence of diarrhea in Fujiwara et al.'s report (13) and the presence of Guillain-Barre syndrome suggested by sural nerve biopsy results in Rouanet-Larrivier et al.'s study (14) strengthen the relationship between these two diseases.

Diabetic polyradicular plexopathy, insulin neuropathy, and chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered in differential diagnosis as well.Insulin neuropathy is an intensive, acute, painful neuropathy seen into the 3rd-4th weeks of insulin therapy (16). Since our case has had a history of insulin intake for many years, we did not consider this condition. Diabetic polyradicular plexopathy is a painful neuropathy especially seen in type 2 diabetic patients with unilateral or asymmetric involvement. Power loss is usually to the proximal lower extremities; upper extremity involvement is rare. There is extreme weight loss in its clinical picture (17). Clinical findings of our case were not compatible with this picture either. CIDP is a chronic and progressive condition with relapses. A two-month or longer progression story is required for the diagnosis. It is 11 times more common with diabetes mellitus compared to the general population. Motor symptoms are affected in the foreground and it is a more severe polyneuropathy. Increased CSF protein and absence of cell (albuminocytologic dissociation) are typical for GBS and CIDP. Protein increase starts especially from the second day onwards and reaches its height in the 3rd-4th weeks. We detected increased protein level in our patient in the first week. Prior to hospitalization, our patient did not have additional symptoms other than neuropathic pain; the clinical picture of our patient had started seven days ago and had been acute. Due to his mono-phase clinical picture (compatible with GBS) and ENMG findings, we did not consider CIDP or an onset of CIDP in our patient (18).

CSF pleocytosis and a mixed type of polyneuropathy can be seen in the course of DM. However, we believe that our patient had GBS because of the high level of (141 mg/dL) CSF protein, acute loss of strength in the lower and upper extremities, which is uncommon in the course of traditional DM, and the rapid response received after the IVIG treatment.

Evaluating the 5 cases in the literature (12-15), we see that the condition is more common in women between 25-64. These cases also reveal that antibodies can target the axon or myelin and that GBS initiates within the first two weeks after the onset of DKA (Table 2).

In cases developing diabetic ketoacidosis, patients should be evaluated carefully for GBS if there are clinical symptoms such as muscle strength loss, autonomic findings, and pain along with a previously known diabetic polyneuropathy.

In the pathogenesis of diabetic ketoacidosis and GBS, autoimmune mechanisms are known to play a role and both conditions are triggered by infections. As far as our case is concerned, we think that diabetic ketoacidosis could have lead to the autoimmune response caused by the onset of GBS pathogenesis.

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Table 2. Demographic and clinical characteristics of our patients and the cases found in the literature.

Case	Sex/Age	Onset of clinical symptoms	ENG	BOS Protein	Study
1	F/44	6 days	Demyelinating	High	Rouanet-Larniviere et al. 1994
2	F/25	14 days	Axonal	High	Rouanet-Larniviere et al. 1995
3	F/37	6 days	Demyelinating	High	Fujiwara et al. 1996
4	F/44	2 days	Not known	High	Novielo et al. 2008
5	F/64	4 days	Demyelinating	High	Kanemasa et al. 2011
6	M/35	7 days	Mixed	High	**Our patient**

S: Sex; **A:** Age; **F:** Female; **M:** Male; **ENG:** Electroneurography

CONCLUSION

During the treatment of diabetic ketoacidosis patients with pain in the back, arms or legs along with muscle weakness and autonomic symptoms, GBS should be considered. In such cases, treatment should begin as soon as possible after further examinations. Especially patients developing diabetic neuropathy should be examined more carefully.

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