ACUTE MOTOR AXONAL NEUROPATHY IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE REPORT

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ABSTRACT

Development of acute motor axonal neuropathy (AMAN) in children with acute lymphoblastic leukemia (ALL) is a rare phenomenon and needs to be differentiated from neuropathy induced by chemotherapeutic agents as both require different treatment protocols. The later may warrant adjustments in the chemotherapy regimen. Electrodiagnostic (EDX) studies play the key role in this differentiation. We report here an 11-year-old girl with ALL who presented with signs and symptoms of a rapidly progressive neuropathy diagnosed as AMAN through EDX studies, and achieved a better recovery following timely immunomodulatory therapy, electrical muscle stimulation of the key muscle groups, and therapeutic exercises. The differentiation between AMAN and chemotherapeutics' induced neuropathy through EDX studies is important in children with ALL to initiate timely immunomodulatory therapy for AMAN and avoid unnecessary withdrawal of chemotherapeutic agents.

Key Words: Acute motor axonal neuropathy, Acute lymphoblastic leukemia, Electro diagnostic studies, Guillain-Barre Syndrome.

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INTRODUCTION

Acute motor axonal neuropathy (AMAN) is a pure motor form of Guillain-Barre Syndrome (GBS). This disorder is characterized by its predominant involvement of motor nerves and an electrophysiological pattern suggesting axonal damage[1]. It is uncommon to see GBS in pediatric population with acute lymphoblastic leukemia (ALL) and only few cases have been reported in the literature. It is very important to establish the exact etiology when a patient with ALL presents with symptoms and signs of neuropathy, as the treatment and outcome depends upon the cause and may warrant some adjustments in the chemotherapy protocols. Peripheral neuropathy is an important complication of chemotherapeutic agents including vincristine, cisplatin, oxaliplatin, bortezomib, and paclitaxel[2], and in some cases, this toxicity may limit the use of these drugs. We report here a child with ALL who developed acute onset motor weakness while on induction chemotherapy.

CASE REPORT

An 11-year-old girl was being evaluated for fever, pallor, easy fatiguability, enlarged neck lymph nodes, and splenomegaly. She was diagnosed with pre-B-cell ALL after thorough evaluation and investigations. She was started on induction chemotherapy with prednisolone, daunorubicin, vincristine, and L-asparaginase[3]. In the third cycle i.e. on the 43rd day, she developed rapidly progressive ascending weakness of legs followed by left arm. Facial muscles were spared. She did not have any sensory symptom. On examination, she had 1/5 power in legs and 2/5 power in left arm. The muscle stretch reflexes could not be elicited in legs and left arm while they were depressed in right arm.

Laboratory investigations revealed normal liver function tests and normal levels of creatine phosphokinase, aldolase, and electrolytes. Erythrocyte sedimentation rate was slightly elevated i.e. 35 mm/h (normal: < 20 mm/h). The cerebrospinal fluid (CSF) evaluation revealed[4] white blood cells/mm3 (normal: 0-5 white blood

cells/mm^3) with no blast cells, a protein content of 108 mg/dL (normal: 15- 45 mg/dL), and a glucose content of 63 mg/dL (normal: 50-80 mg/dL). Assays for antibodies to Campylobacter jejuni, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, Mycoplasma pneumoniae, and Human Immunodeficiency Virus were negative.

The electrodiagnostic (EDX) evaluation was carried out on the 5th day of weakness which showed un evocable motor responses in bilateral peroneal nerves and small amplitude compound motor unit action potentials in bilateral tibial and left ulnar nerves (Table 1). Sensory studies were within normal limits. On electromyography, there was no involuntary activity, however, few motor unit action potentials were recordable with reduced recruitment. The F-waves were not recordable in common peroneal, ulnar, and tibial nerves while they were prolonged in median nerves. Thus, the picture was typical of a length-independent AMAN.

The child was administered intravenous immunoglobulins (IVIG) at a dose of 2 g/kg over five days[1]. The electrical muscle stimulation of the key muscle groups in legs and left arm and range of motion exercises of all joints of the affected limbs along with chest physiotherapy was also started.

The weakness began to improve after two weeks. A follow-up study was done after six weeks. There were markedly reduced motor amplitudes in tibial and ulnar nerves bilaterally. Un evocable motor responses in bilateral peroneal nerves with evidence of denervation and re-innervation in many muscles was observed on electromyography. After eight weeks, there was improvement in strength and she started walking with support. After three months, she still had some residual deficits,

Table 1: Electrophysiological evaluation on nerve conduction studies on 5th day of onset

Nerve conduction studies														
Nerve stimulated	**Stimulation site**	**Recording site**	**Amplitude Motor=mv Sensory=µv**			**Latency (ms)**			**Conduction velocity(m/s)**			**F-Wave (ms)**		
			Rt	Lt	N	Rt	Lt	N	Rt	Lt	N	Rt	Lt	N
Median (m)	Wrist	APB	6.8	6.5	≥4	2.9	2.8	≤4.4	59	55	≥49	38	43	≤31
	Antecubital fossa	APB	6.6	5.9		6.1	6.0							
Ulnar (m)	Wrist	ADM	4.5	4.4	≥6	2.5	2.6	≤4.4	59	55	≥49	38	43	≤31
	Below elbow	ADM	3.8	4.2		6.3	6.0							
	Above elbow	ADM												
Median (s)	Wrist	Index finger	27	32	≥20	2.6	2.2	≤3.5	59	58	≥50	-	-	-
Ulnar (s)	Wrist	Little finger	38	35	≥17	1.9	2.1	≤3.1	62	65	≥50	-	-	-
Common peroneal (m)	Ankle	EDB	NR	NR	≥2	NR	NR	≤6.5	NR	NR	≥44	NR	NR	≤56
	Below fibula	EDB												
	Lateral popliteal fossa	EDB												
Tibial (m)	Ankle	AHB	2.4	2.6	≥4	5.8	5.7	≤5.8	39	42	≥41	NR	NR	≤56
	Popliteal fossa	AHB	1.4	2.0		15.1	13.9							
Sural (s)	Calf	Posterior ankle	10.1	12	≥6	3.7	3.9	≤4.4	41	45	≥40	-	-	-

Rt – right, Lt – left, m – motor, s – sensory, N – normal, EDB - extensor digitorum brevis, AHB - abductor hallucis brevis, APB – abductor pollicis brevis, ADM – abductor digiti minimi, NR – not recordable
Note: All sensory latencies are peak latencies; all sensory conduction velocities are calculated using onset latencies; the F-wave latencies represent the minimum F-wave latencies

Table 2: Reported cases of GBS during ALL

Author	Year	Age	Gender	Main clinical symptoms	Time since start of chemotherapy	Chemotherapy regimen	CSF Analysis		NCS/EMG diagnosis	Drugs stopped	IVIG#	Outcome
							Protein	WBCs				
Norman	1987	4	Male	Paresthesias, tetraparesis	19	Vincristine	↑*	N†		Yes	No	Partial recovery
Aral	2001	4	Male	Ataxia, leg pain, hypertension, constipation, paraparesis, facial muscles' paresis	90	6-Mercaptopurine and Methotrexate	↑	N	AIDP‡		Yes	Complete recovery
Ray	2002	7	Male	Pain abdomen, bleeding tendency, pallor, fits, squint, nystagmus, tetraparesis, facial muscles' paresis	24	Vincristine, L-asparaginase, methotrexate, and dexamethasone	-	-		No	No	Death
Ray	2002	3	Male	Pain abdomen, constipation, difficulty micturition, downward gaze palsy, loss of vision, cranial nerve palsies, tetraparesis,	21	Vincristine, L-asparaginase, methotrexate, and dexamethasone	N	N		No	No	Death
Anderson	2002	3	Female	Tetraparesis,	15	Methotrexate, cytarabine, and hydrocortisone	↑	N	AMAN⁋	Yes	Yes	Complete recovery
Vembu	2003	32	Female	Pain right shoulder, spontaneous bruises, lymphadenopathy, splenomegaly, tetraparesis, facial muscles' paresis, sensory loss	21	Prednisolone, vincristine, daunorubicin, and L-asparaginase	↑	N	AIDP	No	Yes	Partial recovery
Perez	2007	19	Male	Bladder dysfunction, erectile dysfunction, paraparesis	53	Dexamethasone, vincristine, cytarabine, and methotrexate	↑	N	AMAN		Yes	Death
Lee	2008	25	Female	Paraplegia	47	Methotrexate, cytarabine, and hydrocortisone	-	-	AMAN	No	No	No recovery
Rajeshwari	2013	6	Male	Fever, pallor, cervical lymphadenopathy, hepatosplenomegaly, tetraplegia, facial muscles' paresis	35	Prednisolone, vincristine, daunorubicin, and L-asparaginase	↑	↑	AMAN	No	Yes	Complete recovery
Rajeshwari	2013	2	Male	Fever, pallor, hepatosplenomegaly, tetraplegia	28	Prednisolone, vincristine, daunorubicin, and L-asparaginase	N	N	AMAN	No	Yes	Death
Gupta	2014	5	Male	Painful erection, pain in legs, difficulty micturition, hepatomegaly, tetraparesis	20	Cytarabine, vincristine, L-asparaginase, and methotrexate	↑	↑	AMAN	Yes	Yes	Partial recovery
Bhushan	2015	10	Male	Easy fatigability, fever, anemia and cervical lymphadenopathy, tetraparesis	25	Daunorubicin, vincristine, prednisolone, and L-asparaginase	↑	N	AMAN	No	Yes	Complete recovery
Current case	2017	11	Female	Fever, pallor, easy fatigability, lymphadenopathy, splenomegaly, triparesis	43	Prednisolone, daunorubicin, vincristine, and L-asparaginase	↑	N	AMAN	No	Yes	Partial recovery

*↑ = Increased † N = Normal ‡ AMAN = Acute motor axonal neuropathy ⁋ AIDP = Acute inflammatory demyelinating neuropathy # IVIG = Intravenous immunoglobulin

but was ambulant without support and continued undergoing therapeutic exercises.

DISCUSSION

GBS is an acute immune mediated polyradiculoneuropathy with many variants. The types described in the literature are axonal and demyelinating[1]. The postulated mechanism for acute neuropathies in patients with ALL is the depletion of regulatory T cells that suppresses auto-reactive T cells, either resulting from ALL or intensive chemotherapy[4]. An immune neuropathy in this setting can be triggered by known infective etiology and sometimes ALL may itself behaves as a viral infection to trigger GBS[5]. Chemotherapeutic agent induced neuropathy is another important consideration in children with ALL. Of all the chemotherapy agents, vincristine is the major culprit of early peripheral neuropathy[2]. Most of chemotherapy induced neuropathies are length-dependent sensory or sensorimotor neuropathies often associated with pain[6]. Generally, good outcome is reported for GBS with immunotherapy in children with ALL[3].

So far only few cases of GBS during ALL have been reported (Table 2). All cases (age: 2-32 years) developed symptoms during chemotherapy of ALL with onset time range of 20-740 days. There were mainly males. Majority of the cases had vincristine in the therapy protocol and were continued with the same during treatment of neuropathy. The motor weakness involved lower limbs in three and all limbs in nine cases. Sensory symptoms were reported in five cases in the form of paresthesias, leg pain, sensory loss, and loss of vision. Albuminocytologic dissociation (elevated CSF protein without an elevation in white blood cells) was present in six cases. On electrophysiological evaluation, seven cases had AMAN and two had acute inflammatory demyelinating polyradiculoneuropathy while three were not evaluated. Eight cases were given IVIG. Four cases had a complete recovery, two had a partial recovery, and two died. Among those who did not receive IVIG, two died, one did not recover at all, while one had a partial recovery.

Our case developed motor weakness involving three limbs starting from the 43rd day of chemotherapy initiation, had no sensory symptoms, was found to have albuminocytologic dissociation in CSF and AMAN on EDX evaluation, and achieved partial recovery after IVIG administration.

In the general population, the recovery after development of GBS depends upon many factors. The factors predicting poor prognosis are older age[7], prior gastroenteritis[7], delayed initiation of immunomodulatory therapy[1], serologic confirmation of Campylobacter jejuni infection[8], axonal variants of GBS[9], unexcitable nerves on early nerve conduction studies[9], and poor total motor score at 7th day of admission setting[7].

CONCLUSION

The differentiation between AMAN and chemotherapy induced neuropathy through EDX evaluation is important in children with ALL to initiate timely immunomodulatory therapies for AMAN. Unnecessary withdrawal of chemotherapeutics can worsen the outcome of ALL. Further studies are required to elaborate the prognosis of AMAN in such settings.

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CONTRIBUTORS

UA conceived the idea, collected information and corrected the initial manuscript. SBA searched relevant literature, wrote the manuscript and carried out bibliography.