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Polyneuropathy in Lithium Intoxication -- A Case Report

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Intoxication of lithium carbonate may present as a multiple systematic dysfunction, but central and peripheral nervous involvement is rare and more troublesome. In the past, there was only one case of lithium intoxication with polyneuropathy reported by Chang et al in Taiwan. We report here an additional 49 year-old man with manic-depressive psychosis. He received lithium carbonate medication treatment for 5 years and developed a severe cerebellar dysfunction and a mild sensori-motor polyneuropathy. Blood lithium level was 1.80meq/l two days after quitting lithium. Nerve conduction velocity studies, electromyography and sural nerve biopsy confirmed the peripheral neuropathy with marked evidence of axonal degeneration. The patient got improvement after quitting the medication and receiving rehabilitation therapy.

Key Words: lithium intoxication, polyneuropathy

INTRODUCTION

Lithium carbonate is frequently used in the treatment of acute mania and prophylaxis for recurrent manic-depressive disorders [1]. The potential side-effects of this medication including renal, endocrine, cardiovascular and gastrointestinal toxicities have been reported [2]. But the most troublesome toxicity is seen with central nervous system involvement [3]. Besides, polyneuropathy following lithium intoxication was rare and there was only one case reported in Taiwan [4]. We report here an additional case of lithium intoxication with severe cerebellar dysfunction, nephrogenic diabetes insipidus and mild polyneuropathy. Electrophysiological and histopathological studies of nerves confirm the polyneuropathy with prominent evidence of axonal degeneration. The neurotoxicity of lithium is distressful and the rehabilitation for this kind of neurological deficit is a challenging task.

CASE REPORT

A 49-year-old man was diagnosed as a victim of manic-depressive psychosis in 1973. He received lithium carbonate 1200-1800 mg/day and haloperidol since 1985. The course of treatment was rather smooth until January, 1991 when he suffered from fever, vomiting, general weakness and drowsy consciousness progressively. Serum lithium level was 1.80meq/1 two days after quitting lithium. Nephrogenic diabetes insipidus was found and the renal function was mildly impaired with mild elevation of BUN (20.4 mg/dl) and Creatinine (2.1 mg/dl). Renal biopsy revealed

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pathological finding of focal global sclerosis, but CSF study and brain CT were reported to be normal.

He regained consciousness two weeks later. Physical examination revealed mild motor weakness of lower limbs and hypesthesia over distal part of four limbs. Tendon reflexes were normal. Severe trunkal ataxia, scanning speech, and dysmetria with choreoathetoid movement were also noted, and he could not sit steadily without support. Motor nerve conduction velocity (NCV) in the peroneal and tibial nerves were mildly slow (Tab.1). There were prominent low amplitude of compound motor action potentials. The sensory nerve action potential of the sural nerve could not be elicited. Electromyography showed mild spontaneous activities and moderate polyphasic motor unit potentials in abductor digiti quinti, first dorsal interosseous and extensor digitorum brevis muscles. Somato-sensory evoked potential and brainstem auditory evoked potential revealed prolonged central neural conduction time. Sural nerve biopsy revealed mild diminution in the population of myelinated fiber with marked evidence of axonal degeneration (Fig. 1).

After quitting medication and receiving supportive treatment, his medical condition became stable. Then he received rehabilitation therapy including strengthening exercise, balance training, and coordination training. Motor and sensory status improved gradually but trunkal ataxia and dysmetria had only slight improvements. Two months later, he could stand up and ambulate with a walkrette independently.

DISCUSSION

Lithium intoxication is not uncommon in patients receiving long-term therapy because of its narrow therapeutic range. Nausea, vomiting, diarrhea and abdominal pain are often the first signs of toxic reactions [5]. Fever with leukocytosis in lithium intoxication has also been reported and it does not necessarily imply infection [6]. Possible risk factors which increase lithium toxicity are old age, high dose of lithium and previous damage to the central nervous system [7]. Major surgery, infection, dehydration, deteriorating renal function of combinded treatment with other drugs such as haloperidol, indomethacin, dilantin and diuretics may also precipitate acute toxicity [8,9].

Neurotoxicity with combination of lithium-haloperidol usage was first reported by Cohen and Cohen in 1974 [10], although some following reports [11] considered that this commonly used combination had no ill effects. In animal studies, lithium ion and haloperidol might act on the same intracerebral dopamine receptors, and it was supposed that they may similarly interact at other sites in humans. Theories regarded that lithium enhanced neuroleptic-mediated dopamine blockade on one hand, and neuroleptics facilitated lithium membrane transport on the other. Frank and John [12] also reported that it was the dosage of neuroleptic administrated, and not the serum lithium level or lithium dose predicted neurotoxici-

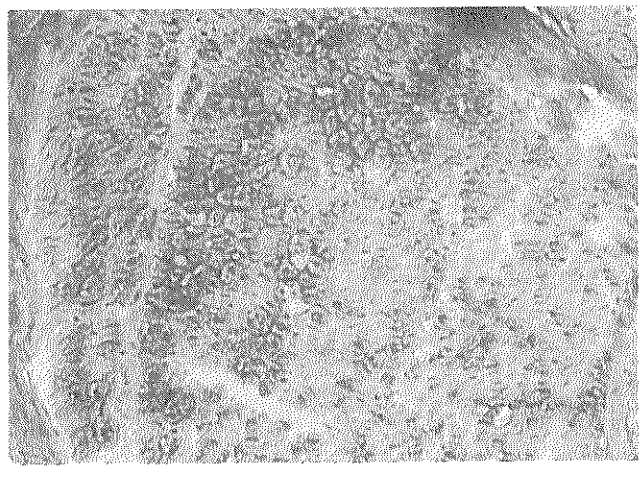

Fig.1 Microscopic view of sural nerve (Modified Gomori-Trichrome stain, 100x) There are mild diminution in the population of my elin fibers with marked evidence of axo nal degeneration.

Table 1. Nerve conduction study

Nerve	Site	MNCV	CMAP	SNCV	SNAP
Median	R	53.4	8*	46.9	12*
	L	52.5	15	46.5	20
Ulnar	R	51.2	7*	40.5	5*
	L	52.7	10	40.7	5*
Peroneal	R	40.4*	6		
	L	39.5*	5*		
Tibial	R	38.4*	9*		
	L	31.1*	12		
Sural	R			abscent	
	L			abscent	

Abbreviations: MNCV=motor nerve conduction velocity (m/sec), CMAP=compound muscle action potential (mV), SNCV=sensory nerve conduction velocity (m/sec), SNAP=sensory nerve action potential (uV), R=right, L=left.
*Pathologic values.

Table 2. Reported cases of peripheral neuropathy after lithium intoxication

	1979 Newman(3)	1979 Brust(13)	1981 Uchigata(20)	1982 Roger(15)	1988 Chang(4)	1990 Geert(14)	1990 Geert(14)	1991 Johnston(21)
Sex/age	F/42	F/18	M/56	M/31	F/27	M/54	F/37	F/69
Dosage (mg/day)	N.D	600	1800	1500-1800	1800	900	1250	1000
Duration	many yrs.	N.D	4 years	many yrs.	many yrs.	many yrs.	3 months	many yrs.
Li level (meq/L)	1.9	0.75	N.D	3.63	3.84	3.5	0.75	1.89
Other drug	N.D	H	L,C	N.D	H	L	H,L	N.D
MNCV/SNCV	decrease	normal	decrease	abscent	decrease	decrease	decrease	decrease
EMG	positive	positive	normal	N.D	N.D	positive	positive	positive
Nerve biopsy	N.D	normal	axonopathy	axonopathy	N.D	N.D	axonopathy	N.D
Motor	plegia	paresis	paresis	plegia	plegia	plegia	plegia	plegia
Sensation	N.D	decrease	decrease	decrease	N.D	N.D	N.D	decrease
DTR	abscent	abscent	decrease	abscent	abscent	abscent	abscent	abscent

Abbreviations: C=chlorpromazine, H=haloperidol, L=levomepromazine, MNCV=motor nerve conduction velocity, SNCV= sensory nerve conduction velocity, EMG=electromyography, DTR=deep tendon reflex, N.D=not done, EMG postive indicated spontaneous activity and/or polyphasic wave

ty. In our case, mild impairment of renal function and combination of lithium with haloperidol might become the precipitating factors for lithium intoxication with severe neurological deficit.

The neurotoxic effects of lithium on the central nervous system have been well documented. It is usually classified as the following three degrees: (1) mild-fine tremor, weakness and lethargy, (2) moderate-muscle fasciculation, ataxia, coarse tremor, dysarthria, incoordination, extrapyramidal syndromes, visual disturbance, confusional state, impaired consciousness, (3) severe-progression of any on the above to coma, seizure, muscular flaccidity, marked cerebellar syndromes, irreversible brain damage and even death [13]. Besides, choreoathetosis is occasionally reported as one toxic effect of lithium therapy. One possible explanation of these abnormal movements in lithium therapy is the hypersensitivity of the dopaminergic receptors in the basal ganglion [7]. Ivan et al [9] reviewed 17 cases of persisting neurologic sequelae following lithium intoxication and found that there were usually signs of damage at multiple sites in the nervous system, but cerebellar features tended to be most prominent. The patient's sex, age, lithium dosage, and maximal blood level of lithium ion did not correlate well with the persistance of the damage. It was also reported that brain lithium content was not always reflected by serum concentration. Because the neurological symptoms might persist or worsen after the serum concentration fell to the therapeutic level. It might also occur in patients whose serum level never raised above 2.0 meq per liter [13]. So lithium-induced neurotoxicity may be related to intracellular, but not serum lithium concentration. Because lithium ion is incorporated into the red blood cells via the active sodium-potassium transport system, the red blood cell levels may be a more accurate reflection of tissue concentrations [5].

In our case, significant cerebellar dysfunction and choreoathetosis movement accompanied by mild sensori-motor polyneuropathy occurred after lithium intoxication. In the past ten years, there have been a few cases of generalized polyneuropathy following lithium intoxication reported (Table 2). Most of the cases manifestated as flaccid paralysis and areflexia [14]. Chang et al [4] had especially mentioned a delayed onset polyneuropathy and considered that there should be other factors except high serum lithium level to trigger the development of polyneuropathy in lithium intoxication. Besides, mild polyneuropathy could be overlooked as the central nervous system damage which was usually more dramatic especially in the early stage of intoxication. Nagaraja et al. [16] found electrophysiologic evidence of axonopathy in six patients with permanent neurologic deficit associated with lithium intoxication who had neither symptoms nor signs of peripheral neuropathy. In addition, subclinical lithium neurotoxicity in patients under lithium therapy without clinical neurological dysfunction was also reported [17-19]. Neurotoxicity was demonstrated by slowing of motor and sensory nerve conduction velocities and prolonged central neural conduction time. The impairments of nerve conduction velocities were correlated with serum lithium level.

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In our case, the electrophysiological study and EMG revealed mild denervation activities and moderate increased polyphasic activities. NCV study revealed only mild slowness of nerve conduction velocities as well as reduced amplitude of the sensory nerve action potential and compound muscle action potential. These indicated an axonal neuropathy and was confirmed by sural nerve biopsy. There were a fwe reports on nerve biopsy of polyneuropathy in lithium intoxication, which revealed mild demyelination with predominant axonal degeneration [14,15,20]. Our findings were compatible with these reports.

Treatment of lithium intoxication include withdrawal of lithium, correction of fluid and electrolyte imbalance, infection prophylaxis and even hemodialysis [8]. Rehabilitation therapy seems to alleviate symptoms and improve performance. Improvement of neurological sequelae could usually be seen over the first 6-12 months after intoxication. And recovery of peripheral neuropathy was usually observed in contrast to persistent cerebellar dysfunction [14].

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鋰中毒引起之多發性神經病變——病例報告

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鋰鹽中毒可引起神經、泌尿，消化、內分泌及心臟血管系統等多方面之功能病變，其中以中樞及周邊神經系統病變最爲嚴重及罕見。我們報告一個四十九歲男性躁鬱症病人於接受鋰鹽治療五年後，因鋰鹽中毒導致重度小腦功能障礙及輕度周邊神經病變。臨床上病人呈現意識障礙、嘔吐、運動失調及不自主運動等症狀，停藥後兩天測得之鋰鹽血中濃度爲1.80meq/1。神經傳導速度檢查顯示於腓神經及脛神經之運動神經傳導速度有輕度減慢，以及複合運動電位波之振幅下降等現象。肌電圖顯示於檢查之伸趾短肌及外展小指肌有自發性顫波及多相波。腓腸肌神經病理切片檢查證實有神經軸突退化及髓鞘減少等現象。經由停藥及復健治療，病人的平衡、運動及感覺功能逐漸有進步，二個月後，病人可藉助行器自己行走。

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