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Lithium treatment of aggressive children and the EEG

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Electroencephalograms (EEG-s) of 44 children aged 6.3—15.4 years were examined at the baseline and 3 months later with two different doses of lithium. Lithium levels in serum in group I. ranged from 0.08 mmol/l to 0.33 mmol/l (mean: 0.23 mmol/l SD: 0.105), and in group II. ranged from 0.40 mmol/l to 0.84 mmol/l (mean: 0.555 mmol/l SD: 0.116). These children represent as Conduct Disorder. EEG-s were correlated across treatment groups with behavioural ratings, ratings of untoward effects, reaction time and different dosages of medication.

In the group I. alpha-recovery time after-eye closing and percentage time of alpha activity in 60 s decreased at unchanged mean alpha frequency. In the group II. both alpha recovery time and alpha activity increased at unchanged mean alpha frequency. Paroxysmal focal abnormalities (spikes, spike-waves etc.) or increase in percentage time of delta activity were not found. Behavioural changes were assessed by using the Pictures Frustration Test for Children of Rosenzweig and the Hamburg Personality Inventory for Children. The group II. were found to be significantly superior to group I. in decreasing aggressive symptoms.

No serious differences were found for the reaction time and side effects as well.

Lithium carbonate has been used for treating agressive adult patients since the 1970s [23, 24, 26]. Good results obtained, called the attention of the child psychiatrists' to it [2, 16, 25, 27]. Though during treatments of adult patients a number of EEG changes have been reported, a very limited number of observations have been published concerning child patients. It was this fact that prompted us to study systematic EEG treatments on hospitalized lithium treated children at our Department. The examinations were carried out according to two kinds of serum level by double-blind tests.

The questions we posed for our study were the following:

1. How frequently are there EEG changes among aggressive patients?

2. Are there specific EEG changes caused by lithium?

3. In case of lower and higher serum lithium levels is there a difference between the possible EEG changes?

4. Is there a connection between a possible EEG change and the behaviour alteration and the cognitive ability, respectively?

Material and Method

For the study 78 asocial aggressive children were treated with lithium carbonate for 3 months. Excluded were those whose anamnesis contained suspected epileptic disease, neurologic disease with focal symptoms, psychosis or mental retardation of a higher degree. The children were hospitalized for 1 month and controlled as outpatients for 2 months. Prior to the discontinuation of medication, they were readmitted to the Department for 2 days for full control examinations. During the month before admittance, the children did not get any psychoactive drug. The dosage was 600—900 mg of lithium carbonate in all the cases and the resulting blood level was tested weekly, then later monthly. 6—10 serum lithium values were obtained per child, and on the basis of the mean values was the grouping formed. At this dose no blood level over 0.84 mmol/l was found, which is very far from the toxic one (over 1.5—2 mmol/l). According to one of our former publications, full internal, neurological and laboratory examinations were carried out for each child (28) and the following psychological examinations were performed: Raven's intelligence test, Hamburg child personality questionnaire, Pictures Frustration Study of Rosenzweig, Dombrose's non-verbal aggression test, Lüscher test, Ranschburg's memory test, reaction timing, tremometric examination and a behaviour rating scale. After evaluating the results, the subjects were formed into 2 groups. In the first group the mean serum lithium level was 0.238 mmol/l (SD: 0.1053), while in the second group the mean serum lithium level was 0.55 mmol/l (SD: 0.1169). In the first group there were 18 males and 2 females with an age (range) of 6—17 years (average: 12.3 years). For the second group 21 male and 3 female patients were selected with an age (range) of 6—17 years (average 11.16 years). Prior to the starting of the treatment and the discontinuing of the medication, out of the 78 subjects EEG examinations were made in 44 cases. For the EEG a 16-channel "MEDICOR" apparatus was used. The evaluation of the data obtained was done by a neurologist with special knowledge of EEG examination who was not given access to the collected data of serum lithium levels and did not take part in the examination of the children. In each case the basic EEG was compared with the one obtained after the treatment and the changes observed were distributed into 3 groups:

1. EEG worsened,
2. EEG improved,
3. EEG changed

While performing the EEG, three parameters were examined:

1. alpha recovery time after closing of eyes,
2. mean average alpha activity in Hz,
3. length of time below 1 min during alpha activity.

Special attention was paid to focal activity, paroxysmal activity or appearance of delta waves.

The EEG activity *worsened* when the alpha recovery time increased, the average alpha activity decreased (in Hz) and the alpha period diminished. But it *improved* when the alpha recovery time decreased, the average alpha activity increased (in Hz) and the alpha period lengthened. It *altered* when only some of the values changed and not in "one direction".

Results

As it can be seen in Table I, among the basic EEGs (resting EEGs) in a near equal rate, 20 and 21% respectively, was pathologic EEG alteration found in the subjects of the study. It was regarded as abnormal EEG when

TABLE I

Basic EEGs in 44 subjects normal vs. abnormal

Group	Normal		Abnormal		Σ	
	n	%	n	%	n	%
I.	16	80	4	20	20	100
II.	19	79	5	21	24	100

asymmetry occurred, especially in the range of delta and theta waves, when paroxismal activity could be observed including spikes and spike wave activity as well as diffuse slowing activity. Naturally, this was related to the age and state of alertness of the child since these factors may strongly influence the alterations.

In the next Table it can be seen that in the I group the alpha recovery time decreased with 30% of the subjects, while with 5% it increased. The average alpha activity decreased in two cases, while it increased in six. The alpha period in 10 cases decreased with 50% of the subjects, while with 25% it increased. The delta and theta activity increased in three cases, while in two it decreased. Increase in paroxismal or focal activity was not observed. In the II group the alpha recovery time increased with two subjects, while with 20 it showed no change. A decrease was observed in two cases. The average alpha activity increased in 6 cases, while decreased with 6. Decreased percentage of alpha activity was observed in eight cases, while increased one was observed in 12 cases. The delta and the theta activities increased in two cases, while in seven cases the activity was reduced. Paroxismal or focal activity appeared in two cases. The alterations were rather in direction than in significance Table II.

In accordance to the criteria previously mentioned, to estimate the improvement and worsening, respectively, the following may be said. In the I group worsening was observed with 15% of the subjects, while no worsening occurred with 85%. However, improvement was not observed at all, while change was found in 25% of the cases. The EEG of 60% of the subjects remained unchanged. In the II group 8.3% EEG worsening was observed, while in 91% the EEG curve did not worsened. Out of this it improved in 12.5%, that is with 3 subjects, changed with 6 subjects — 25% — and remained unchanged in 54.2%, that is with 13 subjects Table III.

DISCUSSION

The opinions on the effect of lithium on the central nervous system are rather contradictory. Reports have been published on its anti-epileptic as well as its epilepsy inducing effect. Erwin et al [5], treated 15 aggressive epileptic patients and in 10 cases they observed the decrease of the number of attacks, while in 1 its increase. With 8 patients the aggressive symptoms also improved.

Gerson, 1960, also mentioned the similar good effect of the drug [7]. However, Jus et al, 1973, and Moore et al, 1981, reported on its oposite effect, who having treated epileptic

TABLE II

Effects of Li^+ therapy on EEGs

Group		Alpha recovery time/s			Mean alpha frequency/Hz			Percentage time of alpha activity in 60 s			Percentage time of delta-theta activity			Paroxismal or focal abnormalities	
		n	%		n	%		n	%		n	%		n	%
	↑	1	5	↑	6	30	↑	5	25	↑	3	15	↑	—	—
I.	=	13	65	=	12	60	=	5	25	=	15	75	=	20	100
	↓	6	30	↓	2	10	↓	10	50	↓	2	10	↓	—	—
Σ		20	100		20	100		20	100		20	100		20	100
	↑	2	8.3	↑	6	25	↑	12	50	↑	2	8.3	↑	2	8.3
II.	=	20	83.3	=	12	50	=	4	16.6	=	15	62.6	=	22	91.7
	↓	2	8.3	↓	6	25	↓	8	33.3	↓	7	29.1	↓	—	—
Σ		24	~100		24	100		24	~100		24	100		24	100

Mean level of serum Li^+ ion: in group I.: 0.23 mmol/l SD : 0.10; in group II.: 0.55 mmol/l SD : 0.11

TABLE III

Effects of Li^+ therapy on EEGs

Group	Worse		Not worse						Σ	
			Better		Different		Same			
	n	%	n	%	n	%	n	%	n	%
I.	3	15	—	—	5	25	12	60	20	100
II.	2	8.3	3	12.5	6	25	13	54.2	24	100

Mean level of serum Li^+ ion: in group I.: 0.23 mmol/l (SD : 0.10); in group II.: 0.55 mmol/l (SD : 0.11)

patients with the drug, observed increasing numbers of attacks and growing aggressivity [14, 18]. A larger number of literary data exists concerning the EEG alterations of lithium treated adult patients with affective psychoses and aggressivity. Czernik, 1978, analyzing the EEG curve of 54 patients, stated that after 1—5 years of lithium treatment at 0.6—1.1 mmol/l serum lithium level, like other psychopharmacons, lithium causes the increase of the paroxismal dysrhythmic pattern, while an already developed abnormal dysrhytmization and the symptoms of disturbed vigilance he regarded as exclusively due to the effect of lithium. When administered simultaneously with other psychopharmacons, these undesirable effects of lithium increase, epileptic potentials may appear, and the number of unchanged curves will significantly decrease. Especially dangerous is the Leponex-lithium combination. The EEG alterations obtained were not in relation with the serum lithium level but rather with the higher blood cell lithium concentration [3]. The former statement was supported by Helmchen, 1971, and Fetzer, 1980, while Prakash, 1982, did not find any significant alteration [9, 6, 19]. Mandel, 1980, and Weiner, 1980, reported that along with lithium electroconvulsive treatment epileptic symptoms were often provoked. They thought that this treatment changed the intake of lithium into the central nervous system and at a normal serum level a toxic quantity got into it [17, 29]. At a higher level than recommended, Herrero, 1973, observed diffuse slow (5—7 cps) wave activity in the EEG and regraded it as a symptom of cerebral dysfunction [11]. Johnson et al, 1970. reported on the acute effect of lithium on the EEG curve. Their findings were based on the treatment of 10 patients. The examinations were carried out before treatment, then 1 and 1/2 hours after administering 750 mg of lithium, and finally, after 7—14 days. In the acute phase only minimum alterations were found with 4 patients, while in the chronic phase they found alterations with 8 patients. They observed, above all, increasing alpha activity, appearance of biliteral deltas and parox-

ismal activity, diffuse slowing down and focal abnormities of various degree. The 4 patients showing slight alterations in the acute phase, produced worse EEG in the course of the chronic phase than those not reacting in the acute phase. The higher the serum lithium level was, the stronger became the alterations [13]. Itil et al, 1971, studied the effect of lithium on 9 patients of 35—59 years old. They observed an increase of slow activity with increased amplitudes with 6 patients and also marked irregularity disorganization along with decrease of alpha activity. The dysrhythmic EEG changes were observed particularly in the beginning of a rather low electroconvulsive lithium level treatment, too. As treatment progressed and with an increase of dosage, the diffuse sharp waves and spikes diminished, amplitude decreased, alpha activity was reduced, and slow activity as well as some fast beta activity increased. The slow frequencies were observable in all brain areas, but predominantly in the anterior leads. The dysrhythmic pattern exhibited the least blocking response to opening of eyes. The EEG alterations did not disappear immediately after the treatment: slow waves, sharp waves and spikes gradually decreased and an increased percentage of alpha activity in the faster frequency range with marked augmentation of rhythmical patterns and synchronization were observed as a rebound effect [12]. Heninger, 1976, treating 18 patients with lithium, stated that the delta activity increase was over 180% and the theta activity increase over 250%. The alpha frequency increase was not significant, the fast I and II frequences remained unchanged. The patients were given lithium for 18 days (as an average) and the mean serum level was 1.1 mmol/l [10]. Reisberg, 1979, summing up the side-effect of lithium, stated that in the first few weeks following the lithium treatment a diffuse slowing was generally observed in the EEG both in the healthy and the diseased population. The 6—9 Hz values were increasing and the 10—20 Hz values decreasing. He cautioned that in case of suspected epilepsy in the anamnesis or when the basic EEG is pathologic, lithium should be given with the greatest care [21]. However, Youngermann, 1978, was of the opposite opinion when he evaluated the cases published in the literature of lithium carbonate treated children and youths. He concluded that lithium carbonate is not contraindicated in cases of positive EEG, epilepsy, mental retardation or previous encephalitis, since among the reported cases, such organic diseases were abundant treatments achieved good results and no side-effects, worth mentioning, were observed. The drug did not provoke epilepsy either [30].

De Long, 1978, treated 12 children with lithium for 3—33 months, the serum level was between 0.5 and 1.2 mmol/l. Slightly abnormal EEG alterations were observed in 4 cases. In 1 case occasional paroxismal slow wave activity was found, while in 1 case occasionally generalized right temporal spikes along slow waves, and in 1

case 14 and 6 cps spikes were observed. With the rest of the patients the EEG findings were normal whether they were awake or asleep [4]. Bennet et al, 1983, examined the EEGs of 48 children treated with lithium or haloperidol, respectively, for 4 weeks. The serum lithium level was 0.32—1.51 mmol/l (mean, 1.03 mmol/l). Before the beginning of the treatment 58% of the children showed abnormal EEGs. Both the lithium treated and the haloperidol treated children showed deteriorating EEGs compared with a placebo treated one. EEG evaluation experts, exclusively on the EEGs were able to separate the three groups from one another. In the lithium group out of 17 children 2 showed pathologic EEGs, while 1 abnormal EEG became normal. In the placebo group out of the 16 children 3 showed abnormal EEGs, while 1 became normal at the end of the placebo period. However, within the normality, when the worsening and improving was under observation, it was found that lithium caused significant worsening in the EEG. [1].

The questions posed in the introduction on the basis of our results, may be answered as follows. The 21% EEG abnormality observed with the aggressive patients — compared with the literary data — may be regarded as average in this population of subjects. [8, 15, 20, 22] Owing to the lithium treatment, with different serum levels, no specific alteration was observed in the EEGs, in regard to this compound. Those alterations, which were observed, could not be related to the serum level of the drug or to the improving aggressive behaviour diagnosed in the psychological examinations While certain authors [3, 6, 9, 17] observed the worsening ot the EEG abnormities due to lithium treatment, Erwin for instance, observed their improvement. In the cases included in our study, the alterations observed pointed towards one or the other of these two directions but never significantly. During the 3 months of treatment at the applied dosage, serious side-effects were not observed either in the biological parameters or in the cognitive abilities, thus, we regard the drug as good for treating aggressive children.

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