ORIGINAL ARTICLE

The Effect of Citicoline Injections on Children with Organic Brain Syndrome Caused by Infection

by

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Abstract

Forty children with organic brain syndrome caused by infections were given Citicoline intramuscular injections. Twenty of these children were within 3 months postencephalitis, the other 20 children were over 3 months postencephalitis. There were statistically significant negative correlations between the length of time from recovery from encephalitis to the initiation of administration of CDP choline and the improvement of many of the symptoms of organic brain syndrome. In other words, these patients who began receiving Citicoline (CDP choline) within 3 months showed greater improvement than those who began receiving CDP choline over 3 months after recovering from encephalitis.

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Introduction

A large amount of clinical evidence indicated the efficacy of cytidine diphosphate choline (CDP choline), injected intravenously or into the subarachnoid space of the spinal cord, in restoring brain activity in patients with traumatic, apoplectic and other disorders of the brain. Double blind studies of CDP choline have been done by many authors [1,2,3,4,5]. All of these studies found that there was a significant difference between CDP choline and the placebo. Since CDP choline introduction into clinical therapy in 1963, until now, there has been no study describing the effect of intramuscular administration patients with organic brain syndrome caused by infection [1,2,3,4,5]. The effects of CDP choline are evident in the improvement of mental and somatic dysfunction. In particular, a marked restoration of consciousness is followed by a proportional improvement of the spontaneous EEG and of general behaviour as well as by a decrease in the brain edema and a progressive alleviation of the clinical symptoms [6]. Such therapeutic effects have been ascribed mainly to a reestablishment of the phospholipid metabolism distorted by the disease or injury. Lecithin, one kind of phospholipid, is the principal constituent of the membranes of the cell, the plasma membrane, mitochondria, endoplasmic reticulum, nuclear membrane, and especially, the myelin sheath of the nerve. Abnormalities in lecithin will eventually impair cellular metabolism extensively. Ozawa, Ishie et al. demonstrated (cited by Shimamoto and Azamaki in 1975) that experimental brain injury resulted in a marked decrease in the brain's phospholipid content, and especially in its lecithin content [7].

CDP choline is formed from the reaction of choline triphosphate (CTP) and phosphoryl choline. CDP choline is an essential intermediate in the biosynthesis of lecithin in the brain. Besides this, CDP choline, according to Yasuhara, Chandra, and Djoenaidi, also has the following effects : (1) increase the synthesis of dopamine; (2) increase the synthesis of acetylcholine in the brain; (3) decrease the level of serotonin in the hypothalamus and brainstem; (4) facilitate glucose metabolism in the brain; (5) assist blood flow in the brain [1,3,6].

It has long been known that cases of encephalitis may present symptoms of psychiatric disturbance. In most of these patients, conciousness was clouded and positive neurological findings were present, so that no diagnostic difficulty arose, at least in differentiating them from cases of acute functional psychosis [8,9,10,11,12]. Economo, however, writing of encephalitis lethargica, mentioned that such patients could present no evidence of impaired conciousness or physical signs, and indeed that the mental changes might be the only symptoms of the disease. He emphasized the initial similarity of these cases to acute schizophrenia, catatonia, or mania [9,11,13,14,15].

Our experience suggested that of the children with symptoms of organic brain syndrome due to sequelae of encephalitis, some had neurological and psychiatric disturbances, but the others had only neurological or psychiatric disturbances. It also suggested that many of these children showed greater improvement when we gave CDP choline within three months post-encephalitis rather than over three months.

Based on the findings mentioned above, we conducted this trial on children with organic brain syndrome due to the sequelae of encephalitis to test the hypothesis that the improvement of patients with organic brain syndrome is correlated with how soon treatment with CDP choline injections is begun.

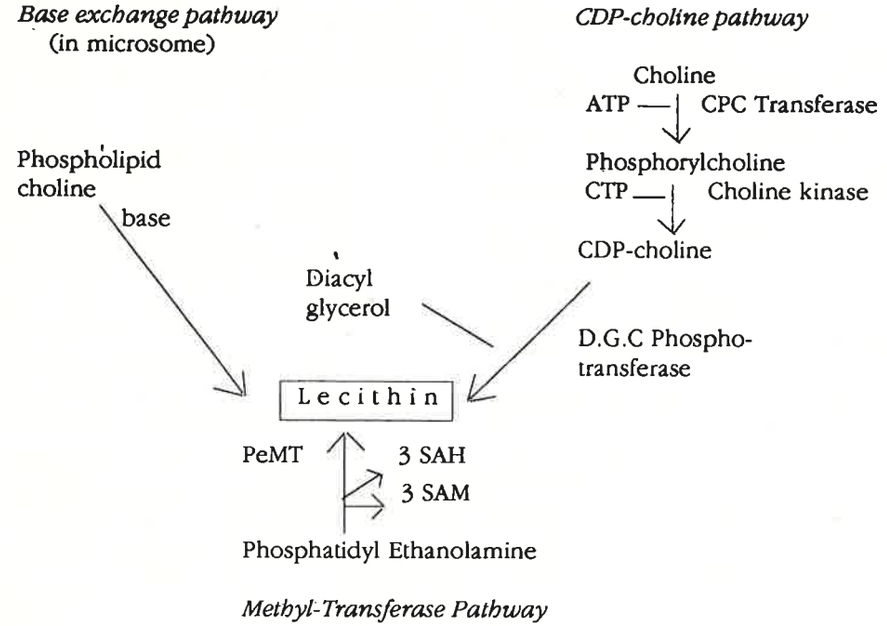

Figure 1. *Pathway of lecithin (phosphatidylcholine) synthesis*

Note :

CTP	=	Choline Triphosphate
CPC	=	Choline Phosphate Cytidyl
DGC	=	1,2-Diacyl Glycerol Choline
PeMT	=	Phosphatidyl Ethanolamine-N-Methyltransferase
3 SAH	=	3 S-Adenosylhomocysteine
3 SAM	=	3 S-Adenosylmethionine

Materials and methods

Our study consisted of 43 children with post-encephalitis or organic brain syndrome caused by infection, 21 children were within 3 months post-encephalitis and the other 22 children were over 3 months postencephalitis. Their ages were between 2 and 12 years, 23 children were boys and 20 children were girls. The patients were admitted to the Psychiatric Department of the Dr. Soetomo Hospital in Surabaya, Indonesia, between January 1, 1984 and January 1, 1990. Before getting infectious diseases, they had both normal behaviour and social development and normal intellectual and motor function. The kinds of infectious diseases were gastroenteritis, measles, varicella, influenza, hemorrhagic fever etc. After they had recovered from these infections, they showed organic brain syndrome. The diagnosis of organic brain syndrome was made according to DSM-III 1980 (diagnostic and statistical manual of mental disorder) [16,17,18,19]. Cases of cerebral palsy or autistic syndrome were excluded from this trial. When convulsive symptoms appeared during this trial, we treated the patients with anticonvulsants.

If the convulsive symptoms remained severe despite this treatment, we stopped giving CDP choline and dropped the patient from the study. All the patients were given intramuscular injections of either 100 mg or 250 mg CDP choline. The average dose was 10-15 mg CDP choline per kg body weight per day. The patients received this drug, once daily, for six weeks (42 days). The effects of citicoline injections on the following psychiatric and neurological symptoms of organic brain syndrome were studied [8,16,17,18,20] : (1) language disorder (expressive and receptive); (2) disturbance in behaviour and social development (e.g. delirium or organic delusional syndrome); (3) disturbance in feeding skills and wetting and soiling control; (4) impaired intellectual and motor function.

We used the kriteria of developmental assessment of Ames to evaluate the improvement of the patients as follows [21]:

Score	Evaluation
0	worse than before treatment
1	no improvement or no change (0-24%)
2	slight improvement (25-49%)
3	moderate improvement (50-74%)
4	good improvement (75-99%)
5	excellent improvement, full recovery, or better than before getting encephalitis.

We worked together with neurologists to confirm the diagnosis of organic brain syndrome and to assess motor function and with a psychologist to assess intellectual function.

Results

Out of 43 patients, 3 cases were excluded from this trial because convulsive symptoms appeared and became severe despite the administration of an anticonvulsants. Of the remaining 40 patients, 20 patients were within 3 months post encephalitis and 20 were over 3 months postencephalitis. We used Spearman's rank difference correlation method, because the samples were small. We counted "t" when the total sample was more than 30.

The background of the trial was shown on Table I,II and III. The effect of Citicoline (CDP choline) on organic brain syndrome caused by infection was shown on Table IV.

Table I. *Age of the children when CDP choline was given*

Age (years)	Post encephalitis: Within 3 months Number of children	%	After 3 months Number of children	%	Total	%
2 - 6	10	50	14	70	24	60
6 - 10	3	15	3	15	6	15
10	7	35	3	15	10	25
Total	20	100	20	100	40	100

Table II. *Sex distribution*

Sex	Post encephalitis: Within 3 months Number of children	%	After 3 months Number of children	%	Total
Boys	13	65	8	40	21 (52.5%)
Girls	7	35	12	60	19 (47.5%)
Total	20	100	20	100	40

Table III. *Age of the children when contracting encephalitis*

Age (years)	Boys Number of children	%	Girls Number of children	%
0 - 5	13	61.9	11	57.9
5 - 10	3	14.3	3	15.8
10	5	23.8	5	26.3
Total	21	100	19	100

Table IV. *Improvement of symptoms by time of postencephalitis*

Post encephalitis (Months)		Number of children scoring: 5	4	3	2	1	0	Total	Statistics
IV.A.	1 - 3	4	13	1				18	r = -0.653
Improvement	4 - 12			1	4			5	t = -5.07
in expressive	13 - 24			1	6	1		8	p < 0.0005
language	25 - 43				4	2		6	(significant)
disorder									N > 30
	N = Total	4	13	3	14	3		37	$t = r\sqrt{\frac{n-2}{1-r^2}}$
IV.B	- 3	3	16	1				20	r = -0.7456
Improvement	4 - 12	1	4					5	t = -6.71
in receptive	13 - 24			2	4	1		7	p < 0.0005
language	25 - 43				4	2		6	N > 30
disorder									
	N = Total	3	16	4	12	3		38	
IV.C	1 - 3		19	1				20	r = -0.750
Improvement	4 - 12			2	3	1		6	t = -6.99
in social	13 - 24			3	4	1		8	p < 0.0005
development	25 - 43				3	3		6	N > 30
	N = Total	0	19	6	10	5		40	
IV.D	1 - 3		14					14	r = -0.7496
Improvement in	4 - 12			1	4			5	t = -6.20
feeding skills	13 - 24			2	4	1		7	p < 0.0005
	25 - 43				3	3		6	(significant)
	N = Total	0	14	3	11	4		32	N > 30
IV.E	1 - 3		9					9	r = -0.564
Improvement	4 - 12			1	3			4	p < 0.005
in wetting	13 - 24			2	4	1		7	(significant)
and soiling2	5 - 43				5	1		6	N < 30
control									
	N = Total	0	9	3	12	2		26	
IV.F	1 - 3	2	14	3	1			20	r = -0.789
Improvement in	4 - 12			1	5			6	t = -7.91
intellectual	13 - 24			1	4	2		7	p < 0.0005
function	25 - 43				1	6		7	(significant)
	N = Total	2	14	5	11	8		40	N > 30
IV.G	1 - 3		5					5	r = -0.4111
Improvement in	4 - 12				2			2	p > 0.05
motor skills	13 - 24				3			3	(not
	25 - 43				2			2	significant)
	N = Total	0	5	0	7	0		12	N < 30
IV.G	1 - 3		5					5	r = -0.4111
Improvement in	4 - 12				2			2	p > 0.05
motor skills	13 - 24				3			3	(not
	25 - 43				2			2	significant)
	N = Total	0	5	0	7	0		12	N < 30

Discussion

Most of the children were between the age 2 and 6 years (50%, 70%) when CDP choline was given (Table I). Table III also shows that the age of the children when they contracted encephalitis were more common in preschool years (61.9%, 57.9%). According to Simmons, younger children were more sensitive to get infectiouns diseases than older children or adult [22]. Table IIpoints out that organic-brain syndrome caused by infection were distributed almost equal in both sexes (52.5%,47.5%). Nelson pointed out that viral infections e.g. measles, varicella, mumps, influenza etc were equally distributed in both sexes and more common in young children (preschool years) [23].

Table IV shows that there were statistically significant negative correlations between the duration of post encephalitis before the beginning of CDP choline injections and the improvement of the symptoms of organic brain syndrome. This correlation held in every category of symptoms except impaired in motor function, may be it was because the samples were too small (N = 12). Hazama and Djoenaidi reported their double blind study about cerebrovascular accident. They found that there was no significant difference between the effect of high dose of citicoline intravenous injection (1000 mg citicoline) and low dose (250 mg or 500 mg citicoline) [1.2].

Summary

Forty children with organic brain syndrome caused by infection had been given citicoline injections intramuscularly, 20 children were within 3 months postencephalitis and the other 30 children were after three months postencephalitis.

The effect of citicoline injections concerning social development, language disorder (expressive and receptive type) feeding skills, wetting and soiling control, intellectual and motoric function were studied.

In this study we found that organic brain syndrome caused by postencephalitis sequelae was more common in preschool years and was equally distributed in both sexes.

We also found that there were statistically significant negative correlations between the duration of postencephalitis before the beginning of CDP choline injections and the improvement of the symptoms of organic brain syndrome, except the motoric function it may be caused by the too small samples.

In this study we have drawn a conclusion that to prevent the sequelae of encephalitis, citicoline injections sholud be recommended given as early as possible for children with organic brain syndrome due to postencephalitis seqeulae.

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