HANDBOOK OF ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

EDITOR-IN-CHIEF A. REMOND

VOLUME 15

Clinical EEG, V

EDITOR: D.D. DALY

University of Texas, Southwestern Medical school, Dallas, Texas (U.S.A.)

PART B

Hereditary, Congenital and Perinatal Diseases

EDITORS: C. DREYFUS-BRISAC AND R.J. ELLINGSON

Hôpital Port Royal, Paris (France) and Nebraska Psychiatric Institute, Omaha, Nebr. (U

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Preface

This Part is devoted to hereditary, congenital and perinatal diseases. It will interest mainly the electroencephalographers dealing with pediatric and neuropediatric problems, and also those working in neonatal intensive care units.

The genetics of EEG anomalies is very important. Many of us have been much concerned by an "abnormal" EEG in a normal child. The first Section throws some light on this field. The genetic approach to the EEG has certainly been minimized so far.

Hereditary and congenital disorders do not give rise to specific EEG anomalies. Among inborn errors of metabolism, phenylketonuria is the most studied. Trisomy 21 is the best known of chromosomal disorders. The EEG data in other chromosomal disorders are scarce. Precise EEG data are still lacking in other congenital malformations as well.

The usefulness of the EEG in patients with prenatal infections is certain, but EEG anomalies are non-specific.

Evoked potential recording aids in early diagnosis of sensory defects secondary to prenatal infections. They are also of interest during the neonatal period where they could help in detection of brain damage.

During the neonatal period the EEG in wakefulness and sleep gives valuable information in cases of metabolic disorders, birth trauma and severe brain damage. Its prognostic value is assessed.

Though many problems remain unsolved, and most of the anomalies are non-specific, this Part will help those who bear the responsibility of interpreting EEGs of neonates and children.

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Section I. The Genetics of EEG Anomalies

A. INTRODUCTION

Among the earliest clinical EEG studies were investigations of large twin series, which showed the human EEG to be genetically determined (Davis and Davis 1936; Raney 1939; Lennox *et al.* 1945). Later, important methodological progress was made when specific EEG phenomena were taken as starting points for research into the genetics of the EEG. Thus Vogel and Götze (1959) showed a simple autosomal-dominant mode of inheritance of the low voltage EEG in an investigation of 117 children from 60 families. Vogel (1962) similarly studied the genetics of beta-activity. These results support a multifactorial mode of inheritance with an age-dependent threshold-gene effect. Furthermore, an autosomal-dominant mode of inheritance of the markedly regular alpha-EEG is probable (Dieker 1967). Research on the genetics of pathological EEG phenomena has mainly been done within the framework of investigations of the genetic basis of epilepsy (see Volume 13A). Essentially new viewpoints on this subject have also been reached by studying the genetics of well-defined specific EEG phenomena, *e.g.*, bilaterally synchronous spikes and waves in resting records and photoconvulsive reactions.

B. GENETICS OF SO-CALLED HYPERSYNCHRONOUS POTENTIALS

Spike-and-wave complexes

Metrakos and Metrakos (1961) investigated siblings and parents of patients with typical and non-typical 2.5–3.5 c/sec spike-and-wave complexes in wakefulness. Overall, 36.8% of the siblings and 7.7% of the parents also showed spike-and-wave complexes in their EEGs, as opposed to only 5% in a control group. Penetrance was shown to be age-linked (Fig. 1), positive findings being most frequent (more than 40%) in the $4\frac{1}{2}$–$16\frac{1}{2}$ year age-group. Continuing these studies Metrakos *et al.* (1966) investigated 82 offspring of probands with spike-and-wave EEGs. Typical EEG findings were found in 35%; the characteristic age-dependency of positive findings was also observed. They concluded that an irregular autosomal-dominant gene with age-dependent penetrance must underlie the so-called centrencephalic EEG. These results were confirmed by Matthes and Weber (1968).

Metrakos and Metrakos (1961) suggest that spikes and waves of different types are genetically similar. However, the authors did not mention in their papers how often the EEG changes in probands and relatives occurred in the resting record, during hyperventilation, and during photic stimulation. Furthermore the results published by Rabending and Klepel (1970) do not support the above hypothesis.

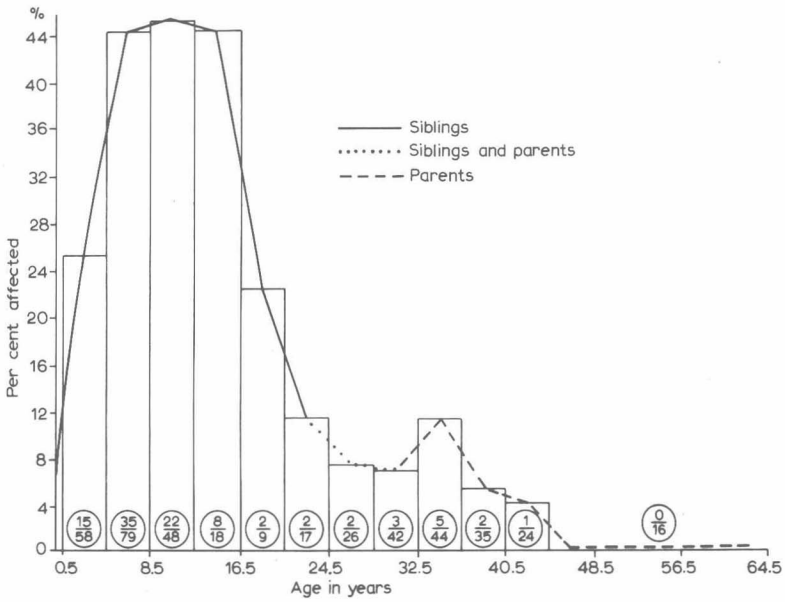

Fig. 1. Age distribution of siblings and parents with a "centrencephalic" EEG (Metrakos and Metrakos 1961).

Rabending and Klepel investigated siblings and parents of patients with 3 c/sec spike-and-wave absences with and without photosensitivity. A photoconvulsive reaction in the EEG was found to be much more frequent in siblings of photosensive propositi. Gerken and Doose (in press) also consider the criterion spike-and-wave to be genetically heterogeneous.

The photoconvulsive reaction

Since the first paper written by Walter *et al.* (1946) many papers have been published on the photoconvulsive reaction (PCR), *i.e.* discharges of irregular spike-and-wave complexes during stimulation with intermittent light.

The pathophysiological basis of the phenomenon is thus far poorly understood. Broughton *et al.* (1969) showed, that in photosensitive individuals, not only visual, but also somatosensory evoked potentials are altered. They concluded that photosensitivity—at least in the epilepsies—"represents a diffuse multimodal alteration in cerebral excitability affecting various levels of different sensory systems". This assumption is supported by the observation that photosensitivity is frequent not only in the epilepsies, but also in patients suffering from neurovegetative disorders, *e.g.*, vasomotor headache, migraine, anorexia nervosa, hyperemesis gravidarum (Doose *et al.* 1969).

In 1950 Nekhorocheff first reported on the occurrence of a photoconvulsive response in siblings. Since then, numerous observations of familial coincidence of the phenomenon and concordant behaviour in monozygotic twins and triplets have been reported. Large scale family investigations were first carried out by Davidson and

Watson (1956) and Watson and Davidson (1957). In 62 % of the 43 families examined, photoconvulsive response was found in one or more members of the family besides the proband. A total of 36 % of 112 relatives of 43 probands, as opposed to only 2 % of a corresponding control group, exhibited a photoconvulsive response. Schaper (1961) obtained similar results. Doose *et al.* (1969, and in press) investigated 390 siblings of 218 photosensitive probands using 662 healthy children from kindergartens and school as controls. Of the siblings, 15.5 % exhibited a definite photoconvulsive response compared with 5.2 % of the controls. Furthermore, 255 siblings of mostly epileptic non-carriers were investigated. A photoconvulsive response was observed in only 5.5 % of cases (Gerken and Doose, in press). Positive findings were slightly more frequent in girls than in boys.

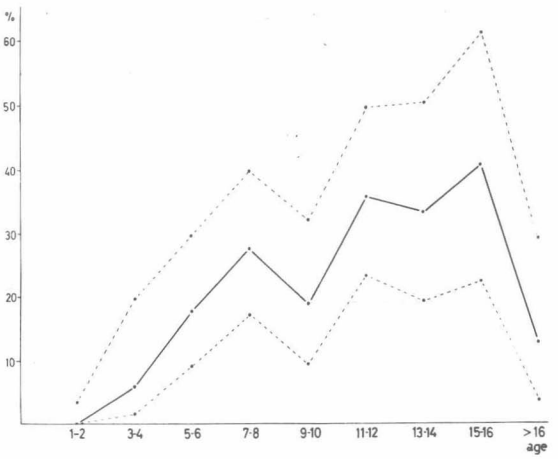

Fig. 2. Age distribution of positive siblings of photosensitive probands [- - - - - = 95 % confidence limits].

Photosensitivity was found to be age-linked, the highest percentage of positive findings being among the 10–16 year old siblings (Fig. 2). The age-linked distribution is similar to that discovered by Metrakos and Metrakos (1961) for spike-and-wave complexes in siblings of patients with a 3 c/sec spike-and-wave EEG. However, a detailed comparison with the results of these authors is not possible, as their papers do not mention how frequently a PCR was found in the siblings.

The age dependency of the photoconvulsive response makes an exact and complete determination of the carriers difficult. Moreover, the phenomenon in individuals known to be positive is not constantly evident, not even in the age groups of maximum penetrance. Hence, carriers of the phenomenon may be more common than can be revealed by a single examination. Because of the methodological uncertainties described above, the mode of genetic transmission cannot be analysed with certainty. Probably an autosomal dominant gene with age- and sex-dependent penetrance is responsible. According to recent investigations of Rabending and Klepel (1970) as well as Gerken and Doose (in press) the genetics of the 3/sec spike-and-wave pattern and the photoconvulsive response seem to be independent of each other.

Rabending and Klepel (1970) included the photomyoclonic reaction in their genetic investigations on photosensitivity. In the relatives they found the same significant differences in frequency for the photomyoclonic response. Only age determines what kind of reaction will be seen in an appropriately disposed individual. Photoconvulsive and photomyoclonic responses are thus different age-dependent symptoms of the same genetically determined hyperexcitability.

The photoconvulsive response can also be a symptom of an organic brain lesion, for instance, metachromatic leukodystrophy. Such sympomatic photosensitivity is a rather rare occurrence. Before accepting such an origin in an individual case, family investigations should be carried out, which possibly will reveal a genetic basis for the condition, even in cases of seemingly symptomatic origin (Gerken and Doose 1969).

Regarding the pathophysiology of photosensitivity, recent investigations carried out in photosensitive baboons (*Papio papio*) are of great interest. In these animals, EEG and clinical phenomena are found which seem to be very similar to those seen in human photosensitivity (Killam *et al.* 1967).

Temporo-central spikes and sharp waves

It was shown by Rodin and Whelan (1960) and Barslund and Danielsen (1963) that temporal focal abnormalities can occur together in the same family as well as concordantly in monozygotic twins. Bray and Wiser (1964, 1965a) published detailed studies of family findings in 40 patients with temporo-central foci. In 30 % of families of the index cases, as opposed to only 5 % of control families, analogous changes could be shown in at least one family member. Specifically, 36 % of the siblings and offsprings and 19 % of the parents were affected (in the control group only 2 % of

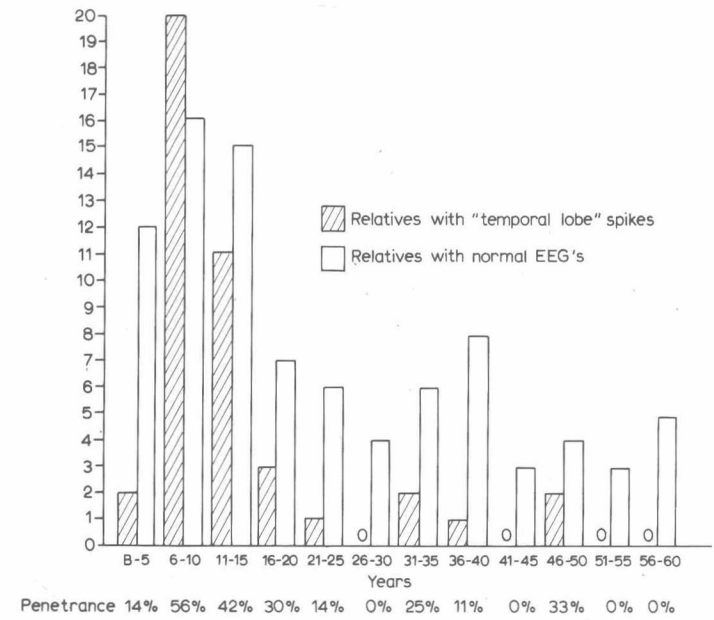

Fig. 3. Age distribution and penetrance of focal "temporal lobe" spike activity (Bray and Wiser 1965a).

each). The phenomenon is characterized by a markedly age-dependent penetrance (Fig. 3) being maximal (up to 50 %) in the 5–15 year age group. The authors suppose that this type of temporal sharp wave or spike focus is caused by an autosomal-dominant gene with age-dependent penetrance. Even bilaterally synchronous discharges were found frequently in these families. In 4 families described in detail by Bray and Wiser (1965b) 5 members had temporal foci, 5 others generalized discharges, and 4 relatives showed both. These findings suggest that there are relationships between the described focal abnormalities and so-called centrencephalic EEG phenomena.

The 14 and 6/sec positive spike phenomenon

In the literature on the 14 and 6/sec positive spike phenomenon familial coincidence and concordance in monozygotic twins and triplets has been reported several times (Millen and Winters 1959; Henry 1963; Ellingson *et al.* 1964; Vogel 1965). Rodin (1964) and Petersén and Åkesson (1968) investigated siblings of carriers. The last mentioned authors found the same phenomenon in 17 out of 32 siblings of children with positive spikes. After correction for age the frequency was 53.1 % in siblings as compared with 9.4 % in controls. No sex difference was found. Thus, positive 14 and 6 c/sec spikes are a genetically determined EEG phenomenon.

C. GENETICS OF ANOMALIES OF BACKGROUND ACTIVITY

Abnormal theta rhythms

Doose *et al.* (1968) studied a special abnormality of background activity, the so-called abnormal theta rhythms. These appear most often in children aged 2–7 years. They are monomorphous 4–7 c/sec waves of constant frequency in the individual case, which interrupt or take the place of the background activity appropriate to the age of the patient (Fig. 4). They appear in bursts especially over the parietal regions (in ear-reference montages) and are seldom diffuse.

These theta rhythms are in many respects similar to the hypnagogic activity characteristic of 1–4 year olds. Whereas the latter occurs mostly in paroxysmal groups extending over all regions of the brain, the abnormal theta rhythms of the waking record are less paroxysmal, and primarily located in the parietal areas. However, a clear differentiation from hypnagogic activity may be impossible without exact information on the state of consciousness of the subject.

Abnormal theta rhythms are not a specific EEG phenomenon but are to be seen most often in the epilepsies of early childhood, particularly in grand mal, myoclonic-astatic fits, absences of early childhood, and febrile convulsions (Doose 1964; Doose *et al.* 1965, 1966; Daute and Klust 1969). Doose *et al.* (1968, and in press) studied 376 siblings of 239 patients with theta rhythms, 101 siblings of mostly epileptic probands without theta rhythms (non-carriers) and a corresponding control group of 615 healthy children. Evaluation of the records was done without knowledge of the subject's status. Theta rhythms were found to be a markedly age-dependent phenomenon (Fig. 5). They occur predominantly in 2–7 year olds, and most frequently between the

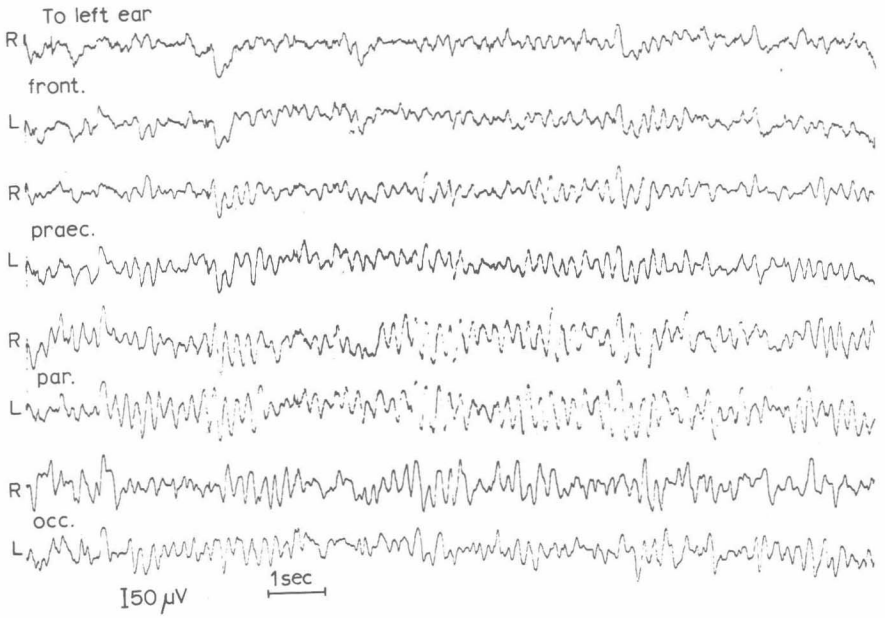

Fig. 4. J.F., male, 4 years, EEG-Nr. 2030/64. Abnormal theta rhythms with parietal accentuation.

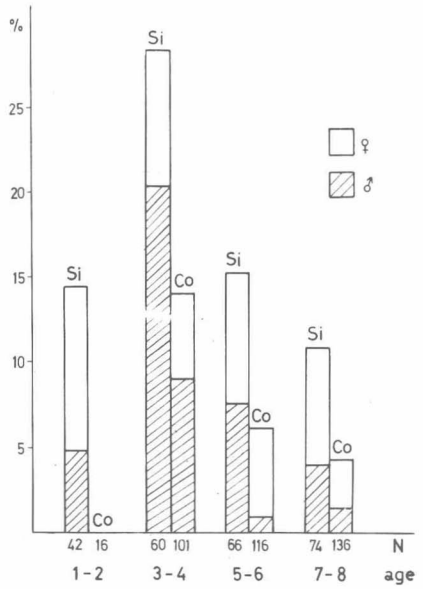

Fig. 5. Age distribution of abnormal theta rhythms in siblings of patients with theta rhytms (Si) and controls (Co). Blind evaluations.

ages of 3 and 5 years. The penetrance was greatest in the 4-year-olds. Theta rhythms were found to be much more frequent in siblings of patients with theta rhythms than in controls (11.4 % as opposed to 5.0 %, $p < 0.0005$). Much interest is aroused by the fact that among 101 siblings of non-carriers there were only 3 who presented typical theta rhythms. Even if the differentiation of theta rhythms from the normal pattern

and in particular from hypnagogic activity is not always possible with certainty, the use of blind technique largely eliminates these sources of uncertainty, since they apply equally to siblings and controls. The highly significant difference in *relative* frequency among the different groups cannot be ascribed to methodological shortcomings. Theta rhythms occur with roughly the same frequency in boys and girls, being slightly more pronounced in boys. Spike-and-waves (in the resting record and during hyperventilation) were seen in 4.5 % of the sibling group and in 1.8 % of the controls. The results suggest that theta rhythms are a gene controlled phenomenon of the resting record and a symptom of an hereditary susceptibility to convulsions of early childhood. Since this symptom cannot be reliably identified by the traditional visual method of evaluation among older siblings and parents, the mode of genetic transmission cannot be analysed with certainty. However, the results obtained to date suggest an autosomal dominant gene with age-dependent penetrance. There are clear correlations with rhythmic changes during hyperventilation. Theta and delta rhythms during hyperventilation are significantly more frequent among the siblings of patients with abnormal theta rhythms than among controls (Doose *et al.*, in press). There are no correlations between theta rhythms on the one hand and delta rhythms in the resting record (see below) and photosensitivity (see page 15B-7) on the other (Doose *et al.*, in press). Theta rhythms thus represent an independent EEG phenomenon.

Occipital 4–5 c/sec rhythms

Nayrac and Beaussart (1956) as well as Pitot and Gastaut (1956) for the first time described abnormal 4–5 c/sec rhythms over the occipital region. A detailed study of this phenomenon was carried out by Kuhlo (1967) and Kuhlo *et al.* (1969). The phenomenon in question is rhythmic 4–5 c/sec waves with amplitudes between 20 and 120 μV and with occipital, occasionally even temporal, localisation (Fig. 6). They are attenuated by opening the eyes. Immediately after closing the eyes a group of alpha-waves can be seen first, and is then replaced by 4 c/sec rhythms. The rhythm can be disturbed by acoustic, tactile, and visual stimuli; it disappears during drowsiness and sleep. The 4–5 c/sec rhythm is seen predominantly beyond the 10th year of life, and occurs mainly in adults. The estimated frequency of trait carriers among the population examined in EEG laboratories is 0.025 to 0.075 %.

Vogel and Götze (1969) found the phenomenon in a monozygotic twin-pair and in three siblings of one family. Kuhlo *et al.* (1969) investigated the relatives of 40 patients with this EEG phenomenon. They found another concordant twin-pair, and demonstrated the 4 c/sec rhythm in 4 of 40 siblings, but not in 30 parents and offspring of carriers. The results suggest a genetic determination in at least a part of the carriers. A simple Mendelian mode of inheritance does not seem to be present. Exogenous causal factors may play a role in some cases (phenocopies).

Parieto-occipital intermittent delta rhythms

Parieto-occipital intermittent delta rhythms are 2–3 c/sec waves of constant frequency and usually of high amplitude (Fig. 7). They are completely attenuated by eye

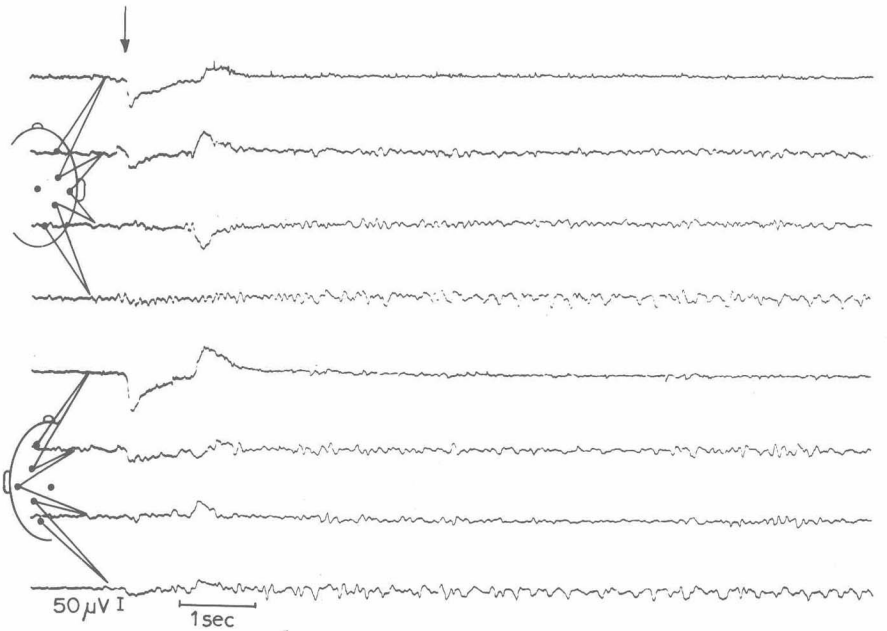

Fig. 6. M.W., female, 33 years, EEG-Nr. 17221/64. Occipital 4–5 c/sec rhythms.

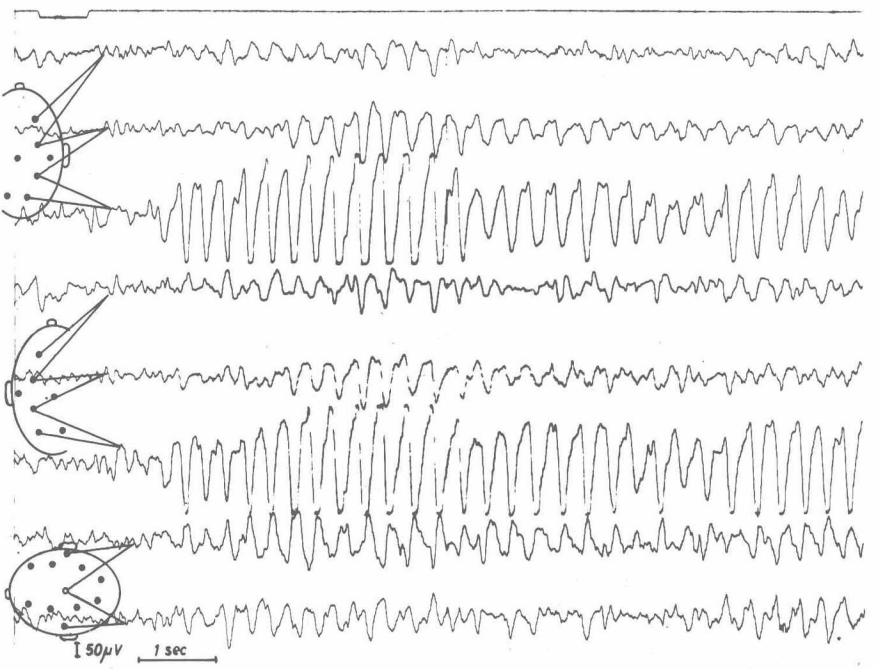

Fig. 7. S.J., female, 6 years, EEG-Nr. 841/67. Parieto-occipital rhythmic 3 c/sec waves.