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Review of juvenile cerebral lipidosis and some observations in two cases

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A REVIEW OF JUVENILE CEREBRAL LIPIDOSIS AND SOME OBSERVATIONS ON TWO CASES

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INTRODUCTION

The lipidoses comprise a number of disorders in which there is a disturbance of lipid metabolism and in which there is an accumulation of lipids in the body tissues. In most of these conditions many portions of the body including the nervous system are involved. Bird (1948) stated that among the disease entities which are characterized by abnormal lipid metabolism are a group which involve the nervous system (amaurotic family idiocy and variants thereof) and a group which usually does not affect the nervous system (Niemann-Pick disease, Gaucher's disease). The latter statement is not in agreement with many workers as a large number of cases has been reported in which the nervous system has been involved. The varieties which involve the nervous system affect primarily the nerve cells, with accumulation in abnormal amounts of the same classes of lipids that are normally present. Bird held that the development of symptoms and progression of the disease seem to be dependent upon the destruction of greater and greater number of cells.

Globus (1942) felt that the disease was basically a form of abiotrophy or agenesis, that "the nervous system of these

children is altered by the disease at the time of birth, and these cells which are poorly endowed with the means to utilize satisfactory (nutritive) material may at some critical moment in their existence no longer be able to subsist and function properly." Since that time other opinions and hypotheses have been expressed and will subsequently be expanded upon, especially with regard to the hereditary aspects, since this disease usually affects more than one member of a family.

Cerebral or cerebromacular degeneration (amaurotic idiocy) is an hereditary lipid disturbance of the cells of the nervous system. According to Grinker et al. (1960) the accumulated fatty substances have been demonstrated to be gangliosides. These lipids normally comprise 0.3% of the solids of the brain, and in this disorder they are increased in varying amounts. For instance, in the infantile form of the disease (Tay-Sachs Disease) the lipid content rises in concentration to 4-8%, replacing cerebrosides in particular.

A widely used textbook (Grinker, Bucy, and Sahs, 1960) describe four forms of cerebral lipidosis, namely the infantile form (Tay-Sachs Disease), the late infantile form, the juvenile form (Spielmeyer-Vogt Disease), and the late juvenile form. In the infantile form the child seems to be without defect at birth and development progresses unremarkably until about 4-6 months of age. Then characteristically the parents note that

the child is very quiet and apathetic and takes little interest in his surroundings. Visual stimuli cease to attract him. An unusual feature is the response to sudden noise, which evokes a severe generalized spasmodic muscular contraction. Another significant finding is a cherry-red spot in the macula brought out by the contrast between the normal red choroidal reflex and the abnormal surrounding retina. The child becomes completely blind and his extremities may be spastic with conspicuous increase in tone and exaggerated reflexes. States of decerebrate rigidity have also been described. As the condition progresses the extremities may become flaccid and completely paralyzed. The diagnosis is essentially based on progressive neurological findings plus a cherry-red spot in the macula.

The juvenile form of cerebral lipidosis is not manifest until the fifth or sixth year. Progressive blindness develops in children with this disease but ophthalmologic findings differ from those of the infantile form in that the cherry-red spot is absent in the former but optic atrophy and pigmentary degeneration of the retina are found. It is often considered that the peculiar isolated affliction of retinitis pigmentosa may be a variant of amaurotic idiocy. Gradually, weakness and atrophy develop and often general convulsions are present. Diffuse cerebral involvement may be manifested by gradual mental deterioration. Death is invariable but not as rapid as in the infantile form.

The late juvenile form of cerebral lipidosis begins between 15-25 years of age and progresses very slowly. Convulsions and mental deterioration are prominent symptoms. Eventually ataxia, tremors, and muscular rigidity develop. The retinae may be normal or may show pigmentary degeneration.

It is the purpose of this paper to discuss the juvenile form of cerebral lipidosis in some detail as a clinical and pathological entity with special emphasis on associated lymphocytic vacuolization and electroencephalographic findings.

JUVENILE CEREBRAL LIPIDOSIS (SPIELMEYER-VOGT DISEASE)

Clinical History

In 1906 H. Vogt described the juvenile form of cerebral lipidosis, noting that this condition occurs in children who have been in the best of health previously and who begin to show abnormalities during the school years usually beginning between ages 6-14. The onset is gradual and the first symptom is progressive blindness associated with atrophy of the optic nerve head. Mental development becomes arrested and there is gradual regression to dementia. Major function (sic) also regresses and the patient ends in complete paralysis which in the majority of cases is spastic. Death occurs in 5-10 years.

In 1907 S. Spielmeyer described 3 cases in which findings similar to those Vogt had described were noted, but Spielmeyer described the presence of retinitis pigmentosa in addition to optic atrophy, and also epileptic seizures in the later stages of the disease. The disease has since been known as Spielmeyer-Vogt disease.

Schob (1924) noted that the onset of the disease tends to occur at the time of the second dentiton after 6 years of age. He described findings similar to those of Spielmeyer and Vogt, and noted that changes in the eye grounds are those of typical retinitis pigmentosa.

Levy and Little (1940) described Juvenile Cerebral Lipidosis as belonging to a group of diseases consisting of primary degeneration of the retina in which there are progressive changes in the neuroepithelium of the retina. Characteristically there is diminution of vision progressing to amaurosis on the approach of puberty. Also there are associated mental changes plus seizures as a consequence of the progressive lipoid degeneration in the cerebrum.

Genetic Aspects

Juvenile Cerebral Lipidosis is expressed as a recessive Mendelian character with high incidence among siblings in affected families (Turner and Donnelly, 1962). This factor is present in the heterozygous form in each of the parents, who cannot be affected by the disease and who must be carriers. The gene seems to be quite widespread among Caucasian people and present also in African and Asian races.

Sjogren (1930) noted that in no case was there evidence of Semitic ancestry in contrast to the infantile form. He estimated the incidence at 1:25,000 at that time. The incidence of heterozygotes is calculated at 0.5 per cent. Rayner (1952) estimated the morbidity risk at 1:40,000 live births. He estimated that heterozygotes, in spite of the rareness of the disease, occur in appreciable numbers, probably exceeding 1:10,000. Males

and females are afflicted about equally often. In a more recent paper Rayner (1962) estimated the morbidity risk at 1:50,000, indicating a diminishing frequency of the disease. He estimated the heterozygote frequency at approximately 1%.

Clinical Findings

Sjogren (1931) described the five stages of the disease as follows:

Stage 1. In this stage is noted visual disturbances in the form of progressive impairment to total blindness. Ophthalmological examination reveals retinitis pigmentosa and optic atrophy. Onset is between 5-8 years with visual impairment progressing to total blindness 1-2 years after onset. The average age for the development of total blindness according to Sjogren is 6.7 years.

Ophthalmoscopic findings in more detail (Hoffman, 1957; Bergaust, 1962) include yellowish discs showing marked optic pallor, almost atrophy, narrowing of the vessels to threadlike size and intense dark retinal pigmentation, especially at the periphery. Macular findings include small pale flecks centrally with a reddish macula outside this and with darker pigmented rings spread over the macular region. More peripherally in the fundus there may be pigmentation of various sorts.

Stage II. In this stage occurs the onset of convulsions

which recur in the form of typical grand mal attacks. The average age for the onset of convulsions is 11 years. Definite mental changes appear, including lack of emotional control, irritability, restlessness, apathy, and retardation. There are associated alterations in speech, including stammering, explosive articulation, and a tendency toward repetitions of words and syllables.

Stage III. In this stage mental deterioration becomes obvious. Notably, attention, memory, and judgment are impaired and the child quickly forgets what he has learned. Personality changes become more striking. The child is entirely disinterested in his environment and is apathetic and irritable. His face is rigid and devoid of expression, but spasmodic laughing and weeping occur. The content of speech is stereotyped and shows a strong tendency to perseveration. Poverty of words and ideas becomes striking, and the child is able to answer only simple questions. Neurological symptoms become evident in that movements are slow, there is atypical rigidity, and anomalies of posture are present. There are characteristic disturbances of gait with short slow steps in which the knees are flexed and the patient does not lift his feet but rather walks with his whole sole on the floor in a shuffling manner. The arms are not swung in walking. Tremors, both resting and intention, are sometimes present. Babinski and Rhomberg signs may be elicited.

Stage IV. In this stage dementia has reached a severe

degree. The child is apathetic with expressionless facies. Speech is limited to a few short indistinct and inarticulate sounds. Apathy may be interrupted by stereotyped restlessness. Prolonged screaming and crying is common. The child's gait deteriorates rapidly and muscle wasting is evident.

Stage V. In this stage the patient is totally demented and paralyzed. He lies helpless in bed, and sphincter control is lost. The muscles are grossly atrophied, and tendon reflexes are hyperactive. The Babinski sign is present. Epileptic seizures are common, and acrocyanosis is marked. Death soon follows at an average age of 18 years.

Very little has been added to the detailed descriptions of Sjogren. Crawley (1957), Gilje and Nissen (1957), and Harlem (1960) emphasized that the diagnosis is based on three findings: (1) diminished vision, (2) epileptic attacks, and (3) progressive dementia. The epileptic seizures have been noted to occur early or late in the course of the disease.

Pathology

The brain is normal size but hardened (Jervis, 1959). The convolutions reveal many gross abnormalities in position and size and often are symmetrical. The ganglion cells are pear-shaped with ubiquitous swelling and nuclear displacement toward the apical dendrite. The cytoplasm is filled with lipid material.

The dendrites are less involved than in Tay-Sachs disease. The axons show no swelling with exception of the axons of the Purkinje cells, in which localized swelling is not uncommon but apparently without lipid material.

In the terminal stage of the disease there is a characteristic sieve-like structure to the cortex. The cells are huge, well-rounded, and have a thick membrane. The nucleus is at one pole and is small in proportion to cell size. The cytoplasm is described as filled with fine dust-like basophilic and argentophilic granules without definite form, embedded in a background of golden pigment. The axons are well preserved and aside from an occasional slight swelling and tortuosity of the fibers, they exhibit no unusual degeneration. The neurofibrils appear normal within the axons. The dendrites have numerous large swellings. Visible degeneration of the myelin sheaths has not been observed, but marked thinning is present. Most of the long descending tracts appear poor in myelinated fibers.

There have been cases in which gross thinning of the folia of the cerebellum has been observed and the granular layer is about half the normal thickness. As mentioned, the Purkinje cells are large and bottle shaped with their dendrites, including all the branches, swollen from the neck of the cell to the cerebellar surface, so that they resemble large branching arteries. The nuclei are pyknotic and blended into a perinuclear dark mass.

The retinal ganglion cells present changes similar to those found in the cells of the brain. There is great reduction in the number of ganglion cells in the retina. Normal cells may be seen late in the course of the disease and transitional stages to the final disintegration of the cells can be seen.

The exact nature of the lesion in Juvenile Cerebral Lipidosis is unknown. Gangliosides are definitely not increased according to Zeman *et al.* (1963) as they are in the infantile form. Because of the similarity between the dense granular lipid bodies and mitochondria, it has been considered that this disease may involve an unlimited accumulation of mitochondrial stroma. This hypothesis has been supported by the observation that the mitochondrial fraction obtained from brain tissue of Juvenile Cerebral Lipidosis patients always contains lipid bodies. The reduction of activity of mitochondrial enzymes in cytoplasm crowded with lipid bodies, as has been shown in histochemical studies, adds to the above evidence.

Yet, the histochemical studies of Bornstein *et al.* (1964) show that the stored material can be considered as a ganglioside. The lack of metachromasia and the resistance of the substance to alcohol and xylol showed that this ganglioside is not in a free state but presumably protein bound. They further showed an increase in the sphingomyelin and cerebroside fraction. Their findings agree with previous work that several lipid constituents

are accumulated within the affected cells.

Electron microscopic studies of brain tissue from patients with Juvenile Cerebral Lipidosis (Zeman et al, 1963) reveals a characteristic network of lipid bodies accumulating in the cytoplasm. These lipid bodies are present in two different types of internal structure; either a densely granular stroma or a multilocular appearance consisting of round, oval and tubular membranes. There is some suggestion that the bodies may be derived from degenerating mitochondria. In the four patients discussed by Zeman the lipid bodies were similar in structure regardless of age but they were distinctly different from the membranous cytoplasmic bodies of the infantile form.

Of additional interest is the imidazole aminoaciduria in this disease (Baldwin, 1962). There is increased excretion of anserine and carnosine in the range of 20-100 mg per day compared to normal levels of 2-7 mg per day. However, further work by Levenson et al. (1964) has shown that these levels vary from time to time even in the same patient, though some patients do excrete carnosine.

LYMPHOCYTIC VACUOLIZATION IN JUVENILE CEREBRAL LIPIDOSIS

Bergaust (1962) reported vacuolization of lymphocytes in varying numbers in several disease states, including Nieman-Pick disease, Tay-Sachs disease, lymphatic leukemia, lymphosarcoma, Hodgkins disease, Hans-Schuller-Christian disease, and juvenile cerebral lipidosis.

The first report concerning vacuolization of lymphocytes in juvenile cerebral lipidosis was by Bagh and Hortling (1948). The reported frequency of this finding was 9 - 56%. The highest percentages were found in cases in which the disease process was furthest advanced. The vacuoles are described as large, round, and regular, and appear as if they have been punched out of the cell. The vacuoles are found in the cytoplasm only and are often so numerous that they almost fill the cytoplasm. No abnormalities have been reported in other types of leukocytes.

These findings were generally confirmed by Rayner (1952), but the frequency of abnormal cells was generally lower than reported by Bagh and Hortling, and there was no correlation between the frequency of vacuolated lymphocytes and the duration and severity of the disease. The parents and siblings of some of the patients were investigated to determine vacuolization in heterozygotes, parents, and siblings. Results suggested that these cellular findings were the result of the same gene that

caused the disease.

Several studies have appeared since 1952, and in some of these studies vacuolization has been reported at as much as 77% of the lymphocyte population.

One of the more recent and comprehensive of these reports was by Rayner (1962) in which lymphocytic vacuolization was studied in patients and their relatives. In this series 500 lymphocytes were counted per patient. In the homozygotes, all of whom were vacuole positive, the vacuolization of the cytoplasm of lymphocytes occurred at a frequency of 21±2%. Nationwide military controls showed an incidence of vacuole-positive individuals as 4.0±1.3% with a mean frequency of vacuolated lymphocytes per individual of 0.9±0.2%. The frequency of vacuole-positive individuals among the parents, healthy siblings, and children of healthy siblings of patients was 95%, 65%, and 31% respectively and vacuolization occurred in about 1% of the total lymphocytes of a large proportion of these healthy relatives. These findings added to his work in 1952 strongly suggest that the occurrence of lymphocytic vacuolization in healthy relatives of patients with juvenile cerebral lipidosis is an expression of the gene for that disease in the heterozygous condition, and in the patients (homozygotes) it is an inherited effect of this gene.

I was able to study this phenomenon in two patients with juvenile cerebral lipidosis (whose case histories are presented

in the section on EEG, below), but was unable to gain permission to study the relatives of the patients. Therefore my study involved the comparison of rates of lymphocytic vacuolization in two patients with the disease with a group of 20 controls. The control group consisted of 20 volunteers of an average age of 17 years and free from organic disease. Both of the patients were 16 years of age. In these examinations 500 lymphocytes were examined for vacuolization in the patients and the controls. The results are presented in Table I.

In the control group there was a mean of 5.75 cells per 500 cells (1.16%) showing vacuolization. There were found 142 abnormal cells (28.4%) in one patient and 169 abnormal cells (33.8%) in the second patient. The patient with the higher number of abnormal cells was in a more advanced stage of the disease.

Table I.

Numbers and Percentages of Vacuolated Lymphocytes per 500 Cells Counted in Controls and Patients with Juvenile Cerebral Lipidosis

Subjects	Vacuolated Lymphocytes	
Normals	Number	Per-cent
1	6	1.2
2	5	1.0
3	5	1.0
4	4	0.8
5	8	1.8
6	6	1.2
7	4	0.8
8	7	1.4
9	8	1.8
10	8	1.8
11	7	1.4
12	7	1.4
13	7	1.4
14	3	0.6
15	6	1.2
16	5	1.0
17	6	1.2
18	4	0.8
19	6	1.2
20	3	0.6
Mean	5.75	1.16
Patients		
J.P.	142	28.4
G.K.	169	33.8

THE ELECTROENCEPHALOGRAM IN JUVENILE CEREBRAL LIPIDOSIS

Crawley (1957) pointed out that the electroencephalographic (EEG) changes in juvenile cerebral lipidosis provide added evidence that this is a disease of the brain which is progressive in nature and degenerative in character. The types of EEG abnormalities which are encountered in the various forms of cerebral lipidosis vary with the age of onset of the disease. The variation is most likely a function of the level of maturity which the brain has achieved when the disease becomes clinically manifest. Progression in clinical disability is accompanied by increase in degree of the EEG abnormality, especially in general disorganization and slowness of the basic rhythms. This is a functional reflection of the progressively greater number of neurons which are being destroyed by the advancing disease process. The character of this abnormality suggests that the disease is degenerative. The EEG, however, is not specifically diagnostic of cerebral lipidosis, since these findings could represent the electrical response of the cerebral neurons to other disease processes.

For example, the EEG patterns in juvenile cerebral lipidosis is indistinguishable from those seen in many patients with phenylketonuria and even idiopathic epilepsy. Rather, juvenile cerebral lipidosis should be considered in patients with such EEG findings in addition to visual problems and if seizures and/or mental

deterioration are present then the diagnosis is more and more probable.

Levy and Little (1940) reported a case with a normal EEG at 11 years and 4 months deteriorating to a marked diffuse slow abnormality with some spike-and-wave complexes at 12 years and 5 months. They noted 6/sec activity in the frontal and central regions, but the alpha rhythm was well defined in the occipital region. Repeated EEGs after one year showed numerous delta waves of slow amplitude.

Lubin and Marburg (1943) noted that the EEG activity was not particularly disorganized and that in some areas no definite abnormalities were noted. Some random slow activity was present particularly in the occipital region though none of this was of great amplitude.

Radermecker (1952) reported on 2 siblings. One showed bursts of hypersynchronous 4/sec activity against a normal background at age 10 years. By age 11 a right hemiplegia had developed and the EEG showed 5-6/sec activity with some sharp waves over the left hemisphere and bursts of diffuse spike-and-wave complexes during hyperventilation. The other sibling showed diffuse poly-spike-and-wave complexes during hyperventilation at 13 years and the same activity spontaneously at 14 and 15 years.

According to Streifer and Landau (1955) the most consistent finding is bilaterally symmetrical and synchronous slow waves, more manifest during hyperventilation.

Crawley (1957) reported on 3 siblings, all of whom showed diffuse 2-3/sec spike-and-wave complexes with some slow background dysrhythmia. In one patient 2 EEGs at a 6 month interval at 9 years of age showed a definite increase in abnormality. Repeated EEGs in the other 2 siblings showed no increase in abnormality. EEG abnormality was least in the 9 year-old, greater in the 12 year-old, and greatest in the 14 year-old.

Meyer and Manning (1961) implanted intracranial electrodes in an 11 year-old patient and observed patterns consisting of bursts of 2 1/2 to 4/sec spike-and-wave complexes, spikes, and slow waves. These bursts were often generalized but could occur in a single area or hemisphere, or amplitude might be greater in one area than another with frequent shifting of the one of greatest amplitude. The corticograms and subcorticograms were reported as "diagnostic of a multicentric focal convulsive disorder with apparent foci at both cortical and subcortical levels."

Five patients suffering from juvenile cerebral lipidosis have been followed at the Nebraska Psychiatric Institute with repeated EEG recordings for periods up to 9 years. These cases have recently been reported by Ellingson and Schain (1965). Two of the cases J.P. and G.K. (upon whom data on lymphocytic vacuolization is reported, above) will be presented in detail, with illustrations of the EEGs of one of them (G.K.).

Case Reports

Patient J.P.: 16 year-old white female. Onset of visual disturbances occurred at 5 years of age with progression to blindness by age 7. Seizures started at age 10. The patient displays retinitis pigmentosa, dementia, and marked emotional disturbances. Motor dysfunction is equivocal. Repetitive speech has not developed. EEG No. 1 was recorded in 1956 at age 8 years, before the onset of seizures. It showed diffuse bursts of 4-5/sec waves of higher voltage than the background activity, maximal in the occipital region. EEG No. 2 was recorded at age 10 at the onset of seizures. It showed diffuse 2 1/2-3/sec slow waves with occasional spike-and-wave complexes. EEG No. 3, recorded at age 11, showed similar activity. EEG No. 4 at age 12 again showed similar activity, but with increase in the prominence of spike-and-wave complexes. EEG No. 5 at age 14 years showed no change. EEG No. 6 at 15 years showed a little more regular background activity than previous EEGs, and clear-cut diffuse high voltage 2 1/2/sec spike-and-wave bursts. EEG No. 7, one month later, was unchanged.

There has been seen a parallel between progression of clinical disease and increasing EEG abnormality over a considerable span of time in this patient.

Patient G.K.: 15 year-old female. Onset of visual disturbances occurred at 7 years, progressing to blindness at 8

years. Onset of seizures occurred at 8 years. The patient displays retinitis pigmentosa, repetitive speech, motor dysfunction, and dementia. Karyotype is normal. The patient has been deteriorating seriously in the last 2 years. EEG No. 1 (Fig. 1) was recorded at the Mayo Clinic in 1959 at age 9 years and it showed bursts of diffuse 2 1/2 to 3/sec slow waves with occasional spike-and-wave complexes. EEG No. 2 (Fig. 2) was recorded in 1963 at age 14, and showed slower background activity and more prominent bursts of diffuse 2 1/2-3/sec spike-and-wave complexes than the previous record. Subsequent to this the patient was hospitalized. EEG No. 3 (Fig. 3) was recorded in May 1964 at age 15 on a day when the patient was having a series of seizures. It showed almost continuous diffuse 3/sec spike-and-wave activity. Later in the EEG a generalized seizure was recorded. EEG No. 4 was recorded in July 1964 on a day when the patient was temporarily clinically much improved. It showed diffuse 3-4/sec spike-and-wave and polyspike-and-wave complexes and polyspikes with irregular slow background activity. EEG No. 5 was recorded 6 months later; it was identical with the EEG of May 1964 except that no seizures were recorded. Again in this case there has been seen a parallel between EEG abnormality and clinical condition.

The other three patients, although followed for shorter periods of time, showed essentially similar progression of degree of EEG abnormality associated with progressive clinical

deterioration.

On the basis of the earlier reports and their own findings Ellingson and Schain concluded that the EEG patterns in patients with juvenile cerebral lipidosis are relatively uniform, consisting of diffuse bursts and runs of 2 1/2-4/sec slow waves and spike-and-wave complexes with occasional variable asymmetry between hemispheres and sporadic focal spikes. They felt that there is good evidence of a progression of EEG abnormality paralleling clinical deterioration. Early EEG abnormality consists largely of bursts of slow waves with or without occasional spikes, and that with time the incidence and amplitude of the paroxysms increase with more spike-and-wave complexes appearing. They suggested that in children with visual disturbances and retinitis pigmentosa plus ~~are~~ EEG of the type described, the diagnosis of cerebral lipidosis is very probable.

SUMMARY

The main purpose of this paper has been to review the known features of juvenile cerebral lipidosis, including historical and clinical aspects with emphasis on lymphocytic vacuolization and electroencephalographic findings.

Juvenile cerebral lipidosis is a distinct disorder of lipid metabolism with a consistent pattern of progressive clinical deterioration and a high incidence among siblings. Pathologically, the exact nature of the lesion is unknown. Prominent changes are present in the cerebrum and the retina.

Two patients were reported upon in same detail. Clinical histories and clinical examination confirmed previously reported details about age of onset, duration and symptoms in this condition. Hematologic investigation supported findings that lymphocytic vacuolization is a prominent occurrence in this disease. The average frequency of vacuolated cells in the patients was 31.1% as compared with 1.16% in the normal controls. Other reports show characteristic patterns of vacuolization distributed among healthy relatives of patients. EEG examinations were found to support earlier reports of diffuse slow wave abnormality progressing to spike-and-wave patterns of increasing severity paralleling clinical progression of the disease.

LEGENDS FOR FIGURES

Figure 1. First EEG of patient G.K. recorded at Mayo Clinic in 1959 (courtesy of Dr. Reginald Bickford). Tracings labelled by Mayo Clinic system. There are fronto-occipital bipolar montages; tracings 1-4, left hemisphere; tracings 5-8, right hemisphere.

Figure 2. Second EEG of patient G.K. recorded at NPI in 1963. Longitudinal bipolar montages. It will be noted that the seizure discharges (spike-and-wave complexes) are more clear-cut and of higher voltage than in Figure 1. Letter code used to label tracings on this and in Figure 3 is as follows: L = left; R = right; F = prefrontal; M = precentral; P = parietal; O = occipital; AT = anterior temporal; PT = posterior temporal.

Figure 3. Third EEG of patient G.K. recorded at Beatrice State Home 4 months after EEG shown in Figure 2. Note continuous diffuse seizure discharge.

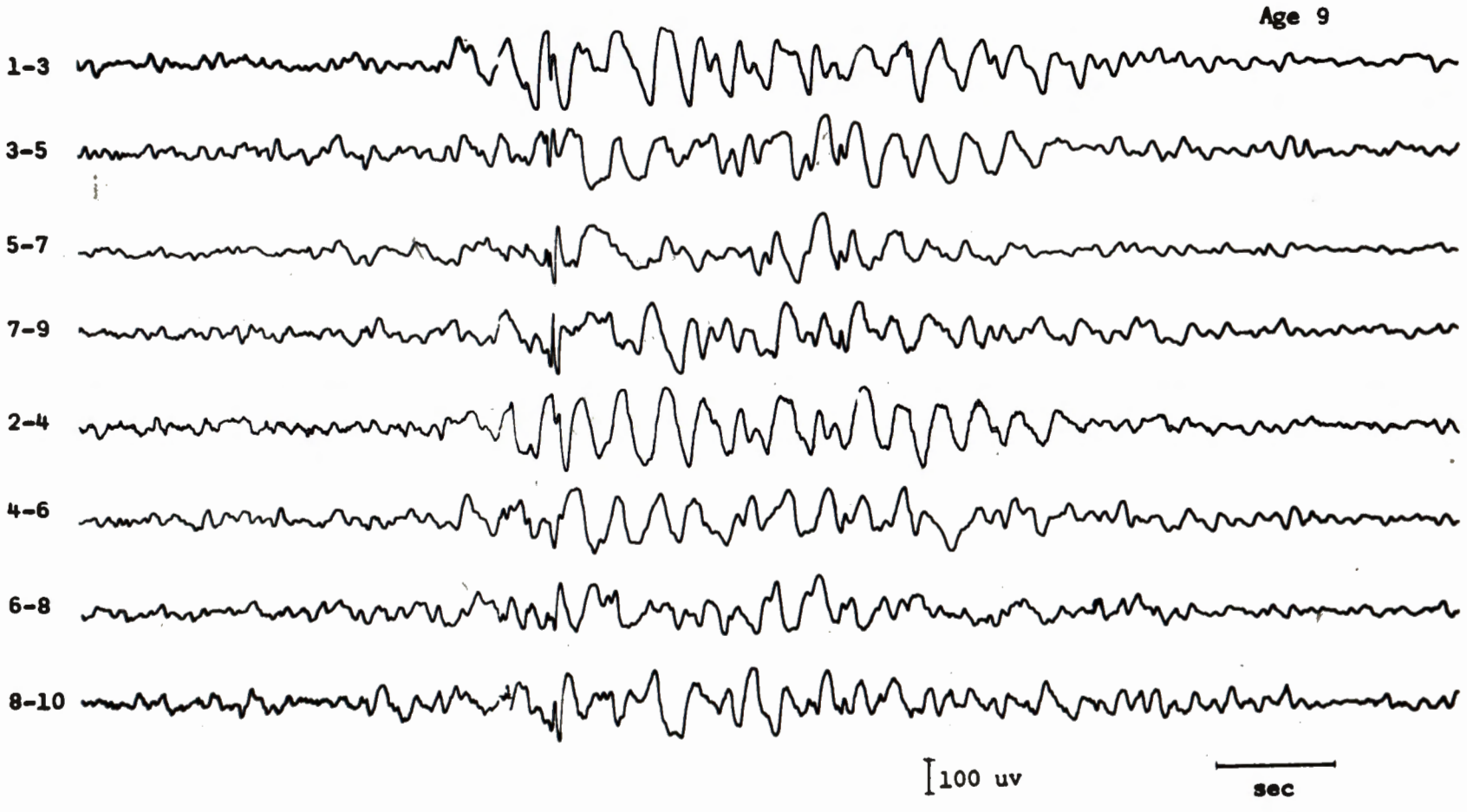

fig. 1

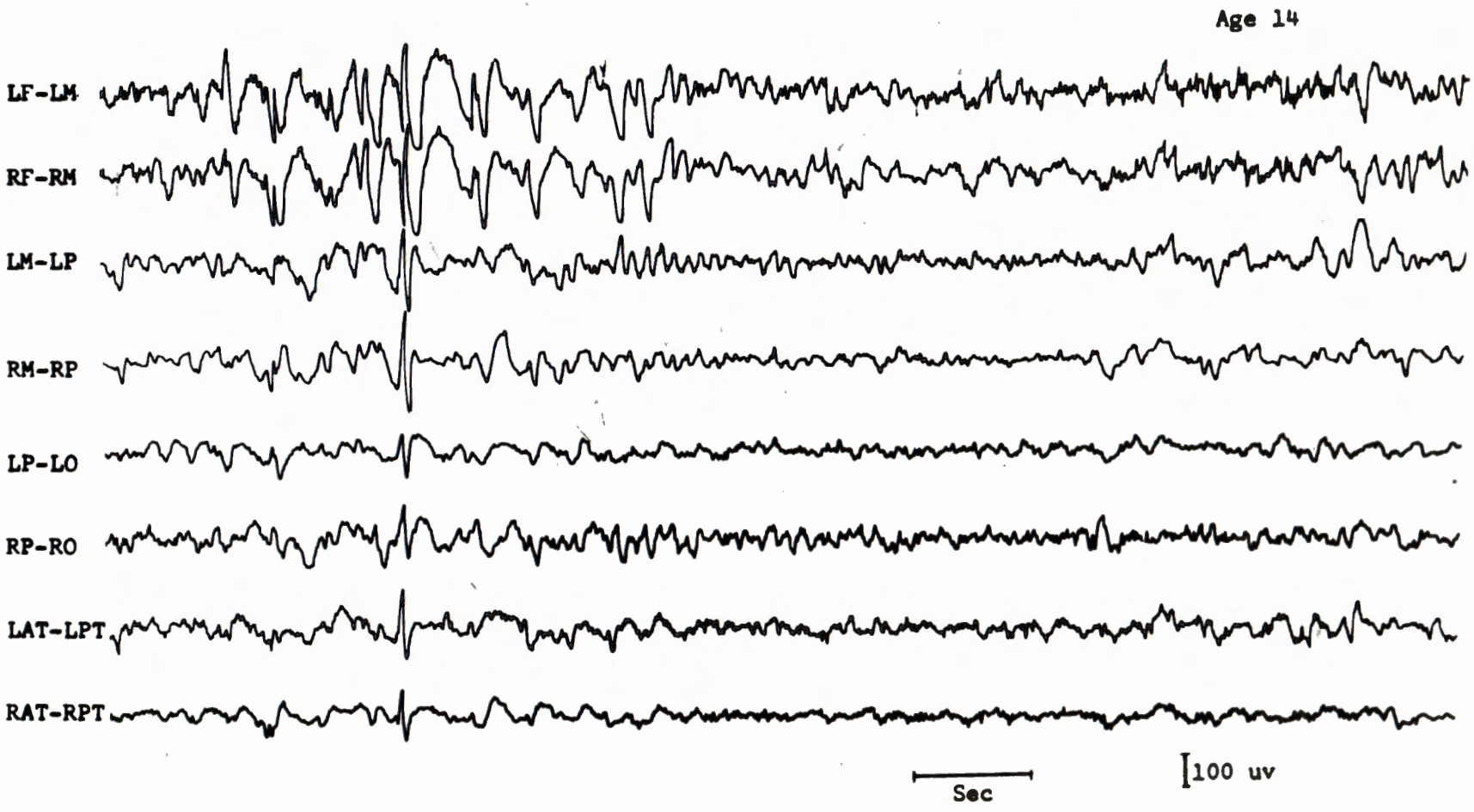

fig. 2

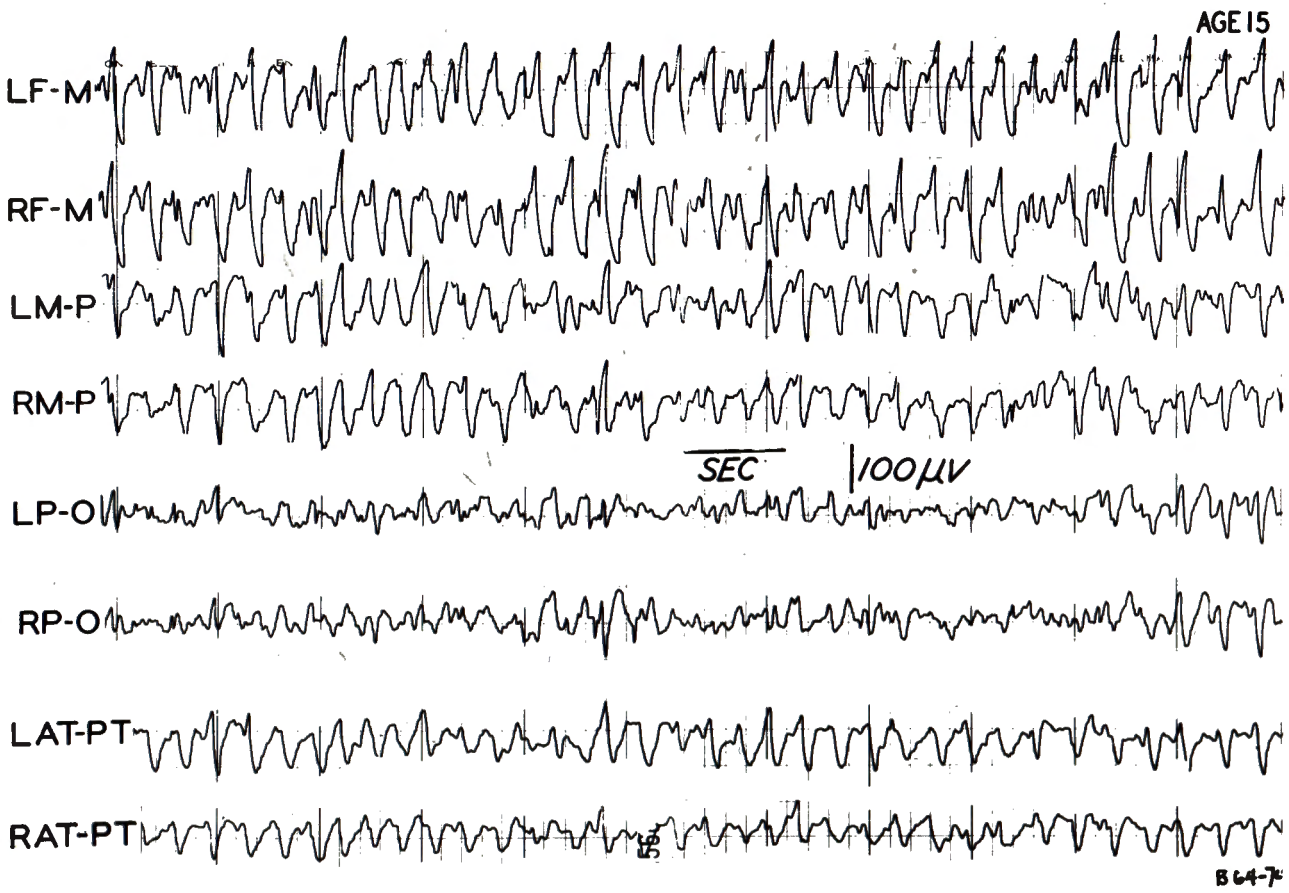

fig. 3

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