Effect of Transplantation of Human Fetal Tissue on Central Nervous System Function in Patients with the Postcastration Syndrome

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Electrical activity of the brain was studied in 45 women after total oophorectomy in a state of calm alertness and in functional overload before and after transplantation of human fetal tissues. Pretransplantation studies showed α-rhythm disorganization, α-activity polyrhythmicity, a tendency toward high-frequency rhythms, and a disordered process of internal synchronization. Studies carried out after human fetal tissue transplantation showed adjustment of the cortex-stem relationships, a reduction of the α-rhythm index, and an increased β-activity index. Reactions to light stimuli and the function of the cerebral cortex improved in the majority of patients after transplantation, this being manifested in appropriate reactions to afferent stimulation. However, by the 6th month posttransplantation electrical activity of the brain was virtually the same as pretreatment.

Key Words: *transplantation of human fetal tissue; total oophorectomy; CNS function after total oophorectomy*

Permanent and paroxysmal psychoemotional and autonomic disorders developing in patients with the postcastration syndrome (PS) indicate involvement of the limbicoreticular complex in the process.

Up to the present time electroencephalography (EEG) has been an adequate method for studies of systemic functional organization of the CNS. Electrical activity of the brain was studied here in 45 patients with PS. EEGs were recorded with a 9-channel ink-writing Nihon Kohden electroencephalograph. Extracranial (bipolar and monopolar) recording of bioelectrical activity with standard leads was carried out in all cases.

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EEGs were recorded in calmly alert patients and in patients exposed to functional overload (rhythmic photostimulation, constant light and sound exposure, dosed hyperventilation). EEGs were assessed visually and using mathematical analysis by plotting histograms after Faure (in 10-sec time periods).

When analyzing the EEGs we paid special attention to features characterizing the activity as a whole: amplitude, presence of a predominant rhythm and its frequency, appearance of changed forms of activity.

It is noteworthy that in none of the patients observed did we find interhemispheric asymmetry or predominance of abnormal activity forms in separately recorded leads. Analysis of the background records of bioelectrical activity permitted us to single out three EEG types.

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Type I electrical activity of the brain was recorded in 19 women; it was characterized by the predominance of EEGs with a reduced α-rhythm, many of which were similar to records of the "awakening reaction" type.

The amplitude of electrical activity and the α-rhythm percent index were markedly reduced in 10 of the 19 patients (the α-rhythm index did not exceed 20%). α-Activity was detected as individual fluctuations or short groups of low-amplitude waves (10-30 μV), or was not discernible visually and could be detected only during histographical plotting of a curve. Rhythmic light exposure sometimes enhanced the α-rhythm, which disappeared after stimulation was discontinued. Occasional outbreaks of correct α-rhythm of the same amplitude were observed in one-third of the women. A characteristic feature was α-rhythm polyrhythmia; frequency fluctuations in the majority of patients were 2-2.5 cycles, sometimes 3-4 (from 9 to 13 Hz). A predominant form of activity (its index varied from 58 to 75-78%) was low-amplitude (15-25 μV) high-frequency β-activity or transitional low-frequency (14-18 Hz) β-rhythm of the same amplitude without or in combination with generalized θ-activity. In one-third of patients slow θ-range activity in the frontotemporal and central areas presenting as individual oscillations noticeably surpassing in amplitude the basic rhythm was sporadic and detected as individual wave forms and small groups of activity. It clearly manifested itself as activity groups during exposure to light stimuli and acquired a generalized pattern. Multiple acute waves and peaklike oscillations were recorded in all areas.

No depression of the basic rhythm was observed in response to the continuous light, and a nonspecific response to stimulus switch on and off was retained for as long as 10-12 exposures. A cortical rhythm restructuring reaction in response to rhythmic photostimulation was observed in a wide range of frequencies (15-22/sec) in two-thirds of patients. In one third of patients the phenomenon of transformation of the presented stimulus frequency in the form of a doubling or tripling of the basic rhythm was observed. Exposure to hyperventilation resulted in half of the patients in an increase of the oscillation amplitude in all frequency bands and of the α-activity index; in the other half the EEG type was unchanged.

Hence, α-rhythm disorganization, α-activity polyrhythmicity, liability to reproduction of high-frequncy rhythms, presence of abnormal activity forms, and disordered internal synchronization are characteristic of a type I EEG. All this indicates enhanced activating effects of median structures of the brain stem.

Type II EEGs were those transitional from type I to type III. They were recorded in 15 women. A clearly manifest α-rhythm with an amplitude of 20 to 85-90 μV was recorded on the EEGs of women in this group. The frequency of α-rhythm varied from 9 to 13 Hz. A trend toward α-rhythm generalization and increased synchronism (α-activity varied from 49 to 59% in the posterior portions of the brain and from 38 to 54% in the anterior portions) was observed. The spatial distribution of the α-rhythm was blurred in 2 cases, and in one patient regional relations were distorted. In the front portions of the brain α-rhythm was alternating with β-activity, whose index varied from 19 to 36%.

θ-Activity was recorded in all areas as diffuse oscillations or group activity not surpassing the amplitude of the basic EEG rhythm. Hypersynchronous θ-activity discharges enhanced by stimuli were recorded in the frontotemporal leads.

Depression of the α-rhythm in response to the first 2-3 exposures to continuous light was observed in the majority of patients; during subsequent light exposures the α-rhythm was preserved. A rhythm restructuring reaction to rhythmic photostimulation was observed in the median frequency band mainly in the posterior portions of the brain.

The number of θ-activity discharges increased in the presence of hyperventilation.

The appearance of synchronous flashes of slow activity in the frontal portions of the brain both spontaneously and, more so, in the presence of functional overload may be regarded as a result of partial blocking of activating effects originating from the reticular formation of the brain stem and of activation of the thalamocortical synchronizing mechanisms.

Type III EEGs were recorded in 10 patients. A characteristic feature of bioelectrical activity at rest in this group was the predominance of a high-amplitude α-rhythm. In 6 women out of 10 α-rhythm amplitude surpassed 110-130 μV. The α-rhythm frequency varied from 8.5 to 13 Hz and was unstable in one and the same patient. No marked differences in α-rhythm frequencies were recorded in the posterior and frontal parts of the brain.

The shape of α-rhythm apices was sharp and split in all the patients. In half of the patients the α-activity index surpassed 75% of the period of α-rhythm spontaneous depression. Zonal differences in α-rhythm were leveled in the majority of patients, and in one-third of patients the α-rhythm was better expressed in the frontal parts of the brain. In the frontotemporoparietal leads bilaterally

synchronous discharges of a 5-8 V θ-rhythm with amplitude 150-220 μV were recorded. Monopolar EEG leads recorded in the majority of patients the rhythms reflecting the activities of the autonomic centers. The phenomenon of rhythm restructuring in response to rhythmic stimulation was not observed in any of the patients. In the presence of hyperventilation bilaterally synchronous flashes of θ-activity became paroxysmal.

Hence, the type III EEG is characterized by a marked increase of the level of activity and a high synchronization of biopotentials in the α-band; bilaterally hypersynchronous discharges of α- or θ-rhythms are generalized or recorded in the frontotemporoparietal leads, external synchronization processes are attenuated, and a reaction to rhythmic photostimulation is absent.

In the light of present-day neurophysiological data such changes are indicative of dysfunction of the upper stem and diencephalic structures of the brain and blocking of the activating systems of the brain stem. Dissociation of the reticulothalamocortical interrelation develops.

CNS function after human fetal tissue transplantation was examined over time (every month) in 39 of 44 women.

Fetal tissue effects were differently reflected on EEGs and depended on the initial functional status of the brain. EEGs with pathological changes expressed most of all in the thalamocortical structures showed adjustment of the cortex-stem relations. In the majority of patients (31 of 44) basal records showed fluctuations of the α-rhythm from 40 to 80%. During the 2nd-3rd months posttreatment a reduction of the α-rhythm index from 60-80 to 58-24% was observed, as well as a rise of the β-activity index from 7.4-9.4 to 31-50.8% and a reduction of the α-rhythm amplitude at the expense of attenuation of the hypersynchronous α-rhythm; a low-voltage (less than 15-20 μV) frequent β-activity was recorded in all leads. Before transplantation β-activity presenting as synchronous symmetrical spindles of β-activity (16-18 per sec with an amplitude of up to 50-60 μV), often in combination with a high-amplitude θ-rhythm, was observed, particularly so in groups II and III. Low-amplitude (with an amplitude of not more than 10-15 μV) β-activity (20-35 per sec) was recorded mainly in the anterocentral leads; such an activity is considered to be a normal component of the EEG. The α-rhythm amplitude in the frontotemporocentral parts was reduced, more distinct zonal differences were detected, and the α-rhythm became more regular and stable. In nearly half of the patients (in 15 of 31) redistribution of the α-rhythm frequency band was observed, and the a-rhythm frequency mode was established, 9-10 Hz (80-85% of the α-rhythm was located in this frequency band), which is characteristic of a normal EEG.

In the rest of the patients no changes in α-rhythm structure were observed. The trend toward splitting of α-rhythm apices disappeared; the shape grew less sharp and sometimes sinusoidal. In cases where the β-activity increase was noticeable, an increase of the diffuse θ-activity index and of θ-rhythm groups with rounded apices and an amplitude of not more than 40-50 μV was observed.

There are reports on the functional role of the θ-rhythm in the general mechanism of the brain reaction as an expression of inhibitory feedback of limbic structures in response to the activating reticular formation for the creation of the optimal level of brain functioning and protection from possible overexcitation.

The increased θ-activity level observed in this patient population may be regarded as a compensatory reaction of the limbic structures of the brain.

The θ-rhythm grew less expressed as the activity of the cerebral thalamocortical structures increased. It is noteworthy, however, that outbreaks of hypersynchronous high-amplitude θ-activity (up to 80-120 μV) and of α-rhythm, which were recorded both generally and bilaterally, persisted over the entire follow-up period in 30 of 31 women; in only one woman did they disappear 2.5-3 months after the treatment was started if recorded at rest but they were manifested during exposure to functional overload. Exposure to hyperventilation did not result during the first 3 months in an enhancement of α-activity outbreaks; these outbreaks were not paroxysmal and were not associated with increased convulsive readiness, as was the case in 12 of 16 patients before treatment.

The reaction to photostimulation improved in the majority of women. A desynchronization reaction to continuous light was observed in half of the women, with force relations intact; one-third of examinees reacted to stimulus switch on and off; in 7 cases α-rhythm blocking was clearly expressed. A restructuring frequency band was observed in 6 patients in a wide frequency range (3-18 Hz) and was diffuse; in 8 women rhythm assimilation was observed in the 6-10 Hz band and was expressed mainly in the temporooccipital portions. In the rest no rhythm rearrangement reaction to flickering light was observed.

In 24 of 31 patients the maximum shifts of electrical activity of the brain were observed 2-2.5 months after transplantation, although a tendency toward such changes manifested itself as early as

during the 1st month. In 5 women the maximal EEG changes were seen 3 months after therapy was started, but a gradual alteration of the pattern of electrical activity was observed as soon as the 4th month: the α-rhythm index increased, as did its amplitude, it became polyrhythmic, its synchronization increased, its spatial distribution obliterated, β-spindles reappeared as well as complex structure outbreaks, paroxysmal outbreaks of θ- and α-activities increased, hyperventilation exposure was associated with convulsive readiness, and reactions to photostimuli deteriorated. By the 6th month posttransplantation EEG patterns were as initially.

Hence, in this patient population transplantation of human fetal tissue suppressed the activities of the hypothalamo-thalamo-cortical structures, thus enhancing the activity of the reticular activating formation of the brain stem.

In 15 patients in whose basal EEGs a reduced α-rhythm was recorded changes of a different nature were observed 2-2.5 months after transplantation of human fetal tissues.

Fetal transplantation led to a decrease of the principal EEG rhythm by several cycles per sec (from 24 to 14-16 per sec); the β-activity index dropped from 75-85 to 35-40%; α-activity became better manifest, and a trend toward intensification of internal synchronization processes was observed, which was reflected in the increase of the α-index by 20-50% (from 10-15 to 33-58%).

The α-rhythm frequency was reduced by 2-3 cycles (from 13-14 to 9-11 Hz). In 7 women 65% of α-oscillations in the posterior portions of the brain and 76% in the central portions were within the range of 9-10 Hz. Previously α-oscillations with split apices acquired a sinusoidal shape, the α-rhythm amplitude increased 1.8 times, the α-rhythm was recorded as individual sites of activity, and, whereas in the basal record the ratio of duration of sites of α-rhythm and β-activity was 1:4, in the course of therapy it became 1:1 or 2:1, these changes being particularly well expressed in the anterocentral portions of the brain; the peaks and sharp waves disappeared.

The number of diffuse oscillations of β- and θ-activity and groups of θ-activity with an amplitude of up to 40-50 μV was either unchanged or increased in cases where the β-activity index remained high. Bilateral synchronous outbreaks of θ-rhythm discharges with an amplitude of 70 to 100 μV, observed before treatment was started, were still recorded.

Cerebrocortical function improved, as manifested in appropriate reactions to afferent stimuli. Whereas pretransplantation the succession reaction was manifest in a wide range of frequencies and was diffuse, after fetal tissue transplantation the rhythm assimilation reaction was detected at flickering frequency 6-15 per sec and only in the parietooccipital portions. Disordered force relations recovered: strong stimuli induced a more manifest effect than weak stimuli, and the desynchronization reaction was better expressed in the posterior portions of the brain; reactivity of the cerebral cortex improved. The time of succession in response to continuous light exposure decreased from 10-15 to 2-3 sec.

Regressive changes were observed during the 4th-5th months posttransplantation in all the examinees who had close anatomophysiological relations with subcortical structures: the β-activity level increased, while the α-rhythm amplitude became less expressed. Cerebrocortical reactivity and lability diminished, and by the end of the 6th month postoperation the pattern of electrical activity of the brain was as preoperatively.

Hence, patients with abnormally enhanced ascending activating effects on the cerebral cortex on the part of the reticular formation, in parallel with the reduction of the cortical effects developed a tendency toward recovery of balanced cortico-subcortical interaction, which is necessary for a normal course of neural processes. The favorable effect of fetal tissue transplantation on cerebrocortical activity seems to be due to limitation of a pathological flow but not blocking of the ascending activating effects, because the activating effect of the reticular formation is sufficient for homeostatic activity of the brain.

In 5 (2.2%) patients transplantation of human fetal tissue did not induce clear-cut changes in the pattern of electrical activity of the brain, even though their clinical status improved. This was probably due to stable enhancement of synchronizing or activating effects or to organic disorders which arose in these brain structures.

The maximal positive effect of human fetal tissue transplantation as evidenced by changes in the electrical activity of the brain which occurred 2-2.5 months after transplantation, persisted for 3 months, and by the 6th month posttreatment the electrical activity of the brain was again as pretreatment. In 2 patients pathological changes in the EEG increased (rebound phenomenon) 6 months posttreatment, this correlating with the clinical data. Reactive changes in the rhythms were most distinct in the anterocentral portions of the brain which are characterized by close anatomophysiological relations with subcortical structures.

Improvement of the clinical picture after human fetal tissue transplantation is associated with

positive changes of the bioelectrical activity of the brain. But this method cannot be considered as being universally applicable, as was well demonstrated in our research. For instance, the procedure is not indicated for patients with a depleted reserve potential of the activating systems of the brain stem, with increased convulsive readiness, or with grave forms of essential hypertension. In such cases human fetal tissue transplantation may turn out to be a factor strong enough to provoke intensification of pathological foci of impulsation.

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Status of the Breasts in Patients with the Postcastration Syndrome Treated by Transplantation of Human Fetal Tissue

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Clinical and x-ray examinations of the breasts were carried out in 45 women with the postcastration syndrome before and after treatment by human fetal tissue transplantation. The results indicate that a drastic drop of the steroid hormones level and increased gonadotropin secretion occurring in patients with the postcastration syndrome lead to the intensification of involution processes no matter what the patient's age. Benign hyperplastic changes in the breasts induced by previous neuroendocrine gynecological diseases gradually regress. Breast examinations carried out 6-8 months after transplantation of human fetal tissue showed no deterioration of any kind. Clinical examinations and interviews of patients showed an improved turgor of breast skin, although mammography failed to detect any changes in the volume of the glands.

Key Words: *transplantation of human fetal tissues; postcastration syndrome; breast*

The function and architecture of the breasts are closely related to the status of the hypothalamo-pituitary-ovarian system. Persistent disorders in one of the components of the chain of hormonal interrelationships may lead to marked morphological changes in the organ. Since the mammary glands are a target organ for sex steroid hormones, a study of their reaction to the cessation of ovarian function in women undergoing bilateral oophorectomy is of practical interest.

Our aim was to study clinical and x-ray features of the breasts in patients with the postcas-

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