Absence of Crossed Inguinal Extension Reflex in Severe Cerebral Hypoxia of Premature Infants

By

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The crossed extension reflex is one of the representative reflexes of the so-called spinal automatism. According to the general view, it can be elicited in adults exclusively under pathological conditions, notably in the presence of a more or less complete spinal transversal lesion. We have found that by means of a technique employed earlier only in animal experiments the reflex could be elicited in premature infants under physiological conditions [4]. The reflex is elicited in the following way. Pressure is exerted on the point where the femoral nerve leaves the inguinal canal; in response, the contralateral leg is extended in the hip and knee joints. However, the foot and toes are not plantarflected, as would correspond to the physiological properties of the extension reflex, but dorsiflected. Electromyography has shown that during the elicitation of the reflex the extensors and flexors of the limb co-contract, *i. e.* what we deal with is the appearance of two reflexes at the same time, called by us a "co-reflex phenomenon".

Further studies have revealed this reflex to disappear in the first year of life, after going through various phases of regression.

Subsequently, we studied the reflex in premature infants under pathological conditions and found that in some cases it could not be elicited. We, then, tried to clarify the cause of this absence of the reflex, and analysed the material collected in the course of one year so that every case, in which attempts had been made to elicit the reflex and which was autopsied later for some other reason, was included in the study, irrespective of the fact whether or not the reflex could be elicited.

These cases were divided into two groups, one in whose members the crossed inguinal extension reflex could be elicited, and a second group where it was lacking. The clinical data for the patients of the latter group showed that during the period of observation more or less severe episodes of asphyxia had occurred, while such conditions had not been observed in the patients in whom it was possible to elicit the reflex. (The whole question will be dealt with in a separate paper after the autopsy material will have been studied in detail.)

Clinical observations have indicated that in the causing of the above mentioned absence of the crossed inguinal extension reflex, cerebral hypoxia may play an important role. In two cases the question has been approached by electroencephalography and detailed post-mortem examination. The present paper intends to present a report on these two cases.

Case Reports

Case 1. K. I., a female premature infant, was born June 16, and died July 1, 1960. At birth she weighed 1000 g, she was cyanosed, asphyxia could be relieved only by continuous O_2-administration. Regular feeding was unfeasible, plasma infusions were given. Crepitation could be heard over the pulmonary bases. The infant was moaning, gasping and showed divergent ocular movements. She gained no weight till June 24, became marasmic, vomited yellowish fluid, the stools were offensive.

June 21. The crossed inguinal extension reflex could not be elicited from either side. On eliciting the flexion reflex a slight dorsiflexion of the feet resulted. EEG: extremely low voltage, mostly "electric silence" in all leads (Fig. 1), with bursts of high amplitude 4/s waves.

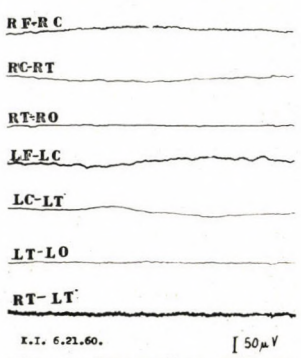

Fig. 1. Case 1. EEG. Extremely low voltage cerebral electric activity, so-called "electric silence"

Abbreviations : R = Right, L = Left, F = Frontal, T = Temporal, C = Central, O = Occipital

July 1. A sudden attack of apnoea developed and the patient died in spite of attempts at pharmacological and mechanical resuscitation.

Gross and Microscopic Anatomy. The brain was underdeveloped, the cerebral cortex revealed cytological patterns and cytoarchitectonics of the prenatal period. In the matrices around the lateral ventricles distended veins filled with blood and extensive venous haemorrhages were visible. There was fresh blood in the cerebral ventricles and in the subarachnoidal spaces. Around the cerebellum remnants of old haemorrhages were intermingled with fresh blood. The cerebral cortex and white matter were pale, and perivascular oedema was present in several areas.

Among the basal nuclei only the periventricular, circular and central median nuclei of the thalamus could be recognized as independent cell groups. In the other nuclei of the thalamus, the entire hypothalamus, the globus pallidus and the putamen the nerve cells were lacking. The upper portion of the medulla (at the level of the facial nucleus) was conspicuously pale. In the lower portion there were hardly staining nerve cells with swollen nuclei. (Fig. 2). The glial nuclei stained well.

In the cerebellum Purkinje's layer disappeared, the internal stratum granulosum was rarefied. The embryonic external stratum granulosum seemed to be intact in some areas, damaged in others (Fig. 3). Ischaemic homogenized nerve cells were seen in the inferior olivary nucleus, and at sites in the cerebellum.

Case 2. B. Zs., a female premature infant, was born June 18, and died June 21, 1960. She was delivered by Braxton—Hicks' version because of placenta previa, with a weight of 1280 g. The lower extremities showed stockinglike haemorrhages. She was moaning, jaundiced, attacks of asphyxia came and went. The heart sounds

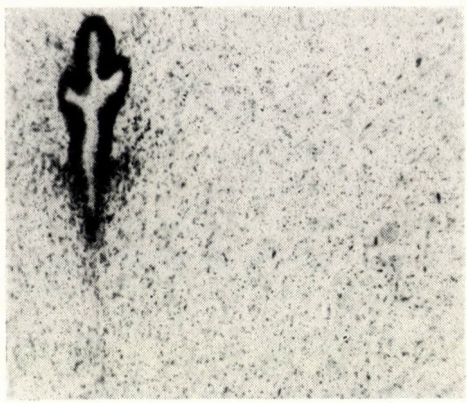

FIG. 2. Case 1. Medulla oblongata. The nerve cells stain weakly, the glia cells take the stain well. Toluidine blue. 10 × 10

were weak but clear. There were tonic convulsions in the extremities.

June 20. The crossed inguinal extension reflex was absent on both sides, the flexion reflex could be elicited on both sides. EEG: "electric silence" with bursts of slow waves of high amplitude (200 μV and more) and 4/s frequency (Fig. 4).

June 21. On lumbar puncture cerebrospinal fluid containing blood was obtained. The condition of the patient deteriorated and she died in spite of many efforts of resuscitation.

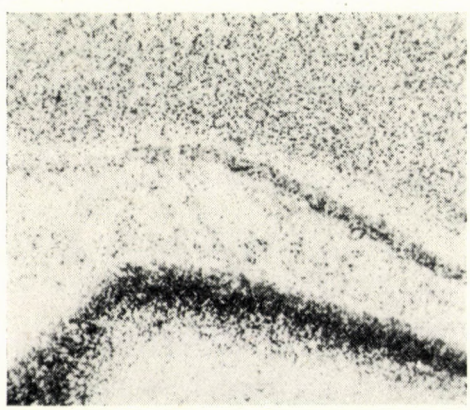

FIG. 3. Case 1. Cerebellar hemisphere. Elective parenchymal necrosis with severe damage to the external stratum granulosum. Toluidine blue. 10 × 10

Gross and Microscopic Anatomy. The brain was primitively developed. There were massive haemorrhages in the leptomeninges and cerebral ventricles. The matrices around the lateral ventricles were thick and contained clotted blood. In the terminal vein a thrombus of lamellar arrangement was found.

Most of the cerebral cortex stained pale, and was rarefied. The cytoarchitecture of the cerebral cortex was very poor, compared with that of Case 1. Only the nucleus but not the cytoplasm of the nerve cells took the stain.

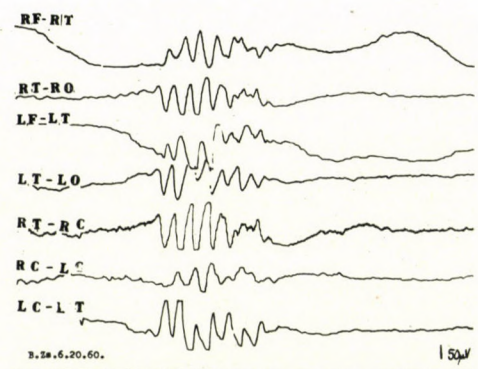

FIG. 4. Case 2. Low voltage cerebral activity with bursts of high amplitude slow waves of 4/s frequency
Abbreviations as in Fig. 1.

The nerve cells of the brain stem stained faintly, but the nuclear groups could be recognized clearly. The inferior olivary nucleus was pale, its lateral curvature was very faint. The external stratum granulosum of the cerebellum was thick and stained well, the molecular layer was low and contained many microglial cells. Purkinje's layer was pale and loose at the basis of some lamellae. In one of the cerebellar hemispheres the internal stratum granulosum was markedly rarefied.

Pathognomonic changes of the nerve cells were not found.

Discussion

The evidence obtained in animal [1, 12, 15] and human [2, 3, 12] experiments, as well as in human pathological cases [19] indicates unequivocally that cerebral hypoxia soon produces changes in the EEG. In complete oxygen lack a total absence of electrical activity is noted simultaneously in all of the cerebral regions within 20 seconds, and in the medulla and cerebellum in 30 to 90 seconds [5]. This "electric silence" is not, however, the first symptom of hypoxia. Preceding its appearance various changes occur in the EEG tracings; frequency and amplitude may increase [5], frequency decrease and high-amplitude delta waves appear [3, 15], and/or synchronization may be noted [15, 16]. As a rule, the appearance of delta waves, and especially the "electric silence", are associated with a more or less severe impairment of consciousness.

As the Figures indicate, in our cases the state of "electric silence" alternated with the synchronization of high-amplitude waves (4/sec). The question may be raised how the lasting state of "electric silence" indicative of a grave disturbance of cortical function was compatible with life, since one of the patients (Case 2) died about 12 hours after the EEG examination, while the other (Case 1) several days later. In this connexion let us mention that

(i) the brain of the newborn baby, and especially that of the premature infant, is remarkably insusceptible to oxygen lack [8, 9];

(ii) according to animal experiments with EEG control, the caudal part of the brain stem [5], especially the reticular formation [14], i. e. the most important autonomic centres, are conspicuously resistant to hypoxia;

(iii) it has been observed [19] that in man a state of "electric silence" of the cortex and thalamus may persist as long as 24 hours with artificial respiration and normal heart activity.

The effect of oxygen lack upon spinal reflexes is well-known. The problem has been surveyed in detail by Kirstein [11].

Still, it was a remarkable phenomenon in the two present patients, and indeed in the whole material under analysis with the exception of just one or two of the severest cases, that the absence of the crossed inguinal extension reflex was associated with a total or partial elicitability of the flexion reflex.

The phenomenon is explained by the animal experiments of van Harreveld and Tyler [7] who studied the flexion and crossed extension reflexes following cord asphyxiation. They observed considerable reflex activity as late as 5 days after 90 minutes of asphyxiation; there was no crossed extension reflex but the flexion reflex could be elicited in all the animal.

In another series of experiments [6] the multisynaptic flexion reflex was more severely damaged by cord asphyxiation than the monosynaptic myotatic reflexes were. According to van Harreveld [6] the presence of internuncial neurons in the reflex arcs of the flexion reflex, and a greater sen-

sitivity of the internuncial neurons to asphyxiation would explain why this reflex was more vulnerable. The long chain of neurons the impulse has to pass may be responsible for the ease with which the crossed extension is abolished by asphyxiation, since this heterolateral reflex has probably more than one internuncial neuron in its arc.

As regards the morphological changes in the central nervous system of the two patients, the two brains were similar concerning their stage of development and the presence of fresh subarachnoidal and intraventricular haemorrhages. There were, however, significant differences between them in the severity and localization of the damage. The lesions in Case 1 were more severe than in Case 2, and they affected predominantly the basal ganglia and the lower part of the medulla. The cerebral hemispheres were relatively preserved. In Case 2 rarefaction of the cerebral cortex was severe, but the nerve cells of the basal nuclei and brain stem were comparatively intact. The ischaemic-homogenizing changes of the nerve cells in Case 1 indicate the pathogenetic significance of the anoxic-vasaldisturbance. Ischaemic erve cells were found, however, only in small numbers, so that the absence and/or faint staining of the nerve cells could not be ascribed solely to anoxic-vasal alterations. The paucity of reserves, the low serum protein level characteristic of the premature infant [8], may have also been responsible for the cerebral haemorrhages, oedema and anoxic-vasal lesions. The underdevelopment of embryonic blood vessels might be a further factor involved. In Case 1 the general weakness of circulation might have been due to the severe changes in the lower portion of the medulla, that *in vivo* may indeed have caused a further increase in severity of the circulatory disturbance.

In Case 2 there were few changes in the nervous tissue, and the lack of anoxic-vasal changes was remarkable. Since the child had several attacks of asphyxiation as well as serious EEG changes ("electric silence"), this peculiar phenomenon needs explanation. In this respect the evidence reported by Titrud and Haymaker [17] is interesting, in that in seven fatal cases of cerebral anoxia from high altitude asphyxiation with rapid death the pathological findings were "of no moment". Környey [13] described two fatal cases of strangulation in which death occurred in approximately 48 hours with relatively few changes in the nerve cells. In our case, however, we deal with a premature infant born with a weight of 1280 g (Case 2), and, as it has been pointed out, prematures are much less susceptible to hypoxia than adults.

In view of all these it may be understood why in this case (the patient lived three days only) the hypoxia had no time to produce characteristic morphological changes in the nervous system.

The clinical analysis of our cases, and also the data obtained in several similar cases under study, indicate that the absence of the crossed ingui-

nal extension reflex (which is regularly present in normal premature infants) must be considered a clinical manifestation of severe cerebral hypoxia and may prove suitable as a clinical test of such states.

Investigations are in progress to study the connexion between the grade of cerebral hypoxia and the absence of the crossed inguinal extension reflex, and also between the EEG changes and the absence of the reflex.

Summary

The crossed inguinal extension reflex, which is regularly elicitable in normal premature infants, was lacking in premature infants with severe cerebral hypoxia. In the two cases studied the EEG showed a so-called "electric silence" alternating with synchronization of bursts of high amplitude slow waves of 4/s frequency.

Gross and microscopic evidences of anoxic-vasal changes were found postmortem in one of the cases, but not in the other, presumably because in the latter there had not been time for the changes to develop.

References

1. Ajmone-Marsan, C., Fuortes, M. G. F. : Electrographic Study of the Convulsant Action of Intravenously Administered Acetylcholine. Electroenceph. clin. Neurophysiol. **1,** 283 (1949).
2. Beigel, A., Haarstrick, R., Palme, F.: Luftf. Med. **7,** 305 (1942). Cit. Jung, R. Hirnelektrische Befunde bei Kreislaufstörungen und Hypoxieschäden des Gehirns. Verh. dtsch. Ges. Kreisl. Forsch. **19,** 170 (1953).
3. Davis, P. A., Davis, H., Thompson, J. W.: Pressure Changes in the Human EEG under Low Oxygen Tension. Amer. J. Physiol. **123,** 51 (1938).
4. Fényes, I., Gergely, Ch., Tóth, Sz.: Clinical and Electromyographic Studies of "Spinal Reflexes" in Premature and Full-Term Infants. J. Neurol. Neurosurg. Psychiat. **23,** 63 (1960).
5. Gänshirt, H., Dransfeld, L., Zylka W.: Das Hirnpotentialbild und der Erholungsrückstand am Warmblütergehirn nach kompletter Ischämie. Arch. Psychiat. **189,** 109 (1952).
6. Harreveld, A. van: Reflexes in the Anterior Tibial Muscle after Cord Asphyxiation. Amer. J. Physiol. **142,** 428 (1944).
7. Harreveld, A. van, Tyler, D. B.: The Influence of Temperature on Spinal Cord Damage Caused by Asphyxiation. Amer. J. Physiol. **142,** 32 (1944).
8. Kerpel-Fronius, E.: Oxigénhiánynyal járó állapotok a csecsemőkorban. M. T. A. Orv. Oszt. Közlem. **3,** 249 (1952).
9. Kerpel-Fronius, E., Varga, F., Kun, K.: Cerebral Anoxia in Infantile Dehydration. Arch. Dis. Childh. **25,** 156 (1950).
10. Kessler, M., Hailman, H., Gellhorn, E.: Studies on the Effect of Anoxic Anoxia on the Central Nervous System. Amer. J. Physiol. **140,** 291 (1943).
11. Kirstein, L.: Early Effects of Oxygen Lack and Carbon Dioxide Excess on Spinal Reflexes. Acta physiol. scand. **23,** Suppl. **80,** 1 (1951).
12. Kornmüller, A. E., Palme, F., Strughold, H.: Über Veränderungen der Gehirnaktionsströme im akuten Sauerstoffmangel. Luftf. Med. **5,** 161 (1941).
13. Környey, St.: Histopathologie und klinische Symptomatologie der anoxisch-vasalen Hirnschädigungen. Akadémiai Kiadó, Budapest 1955.
14. Noell, W. K., Dombrowski, E. B. (1947) Cit. Gastaut, H., Fischer-Williams, H.: Electroencephalogra-

phic Study of Syncope. Lancet **1,** 1018 (1951).
15. Noell, W. K., Kornmüller, A. E.: Zur Sauerstoffmangelwirkung auf die Hirnrinde. Pflügers Arch. ges. Physiol. **247,** 685 (1944).
16. Sugar, O., Gérard, R. W.: Anoxia and Brain Potentials. J. Neurophysiol. **1,** 558 (1938).
17. Titrud, L. A., Haymaker, W.: Cerebral Anoxia from High Altitude Asphyxiation. Arch. Neurol. Psychiat. (Chicago) **57,** 397 (1947).
18. Veith, G.: IV. International Congress of Neuropathology, München, (1961). Thieme, Stuttgart (1961).
19. Wertheimer, P., Jouvet, M., Descotes, J.: A propos du diagnostic de la mort du système nerveux. Presse méd. **67,** 87 (1959).

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