Birth asphyxia and delta response to over-breathing in non-epileptic children

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Although the most common response to over-breathing is the appearance of high-voltage slow rhythms of 2-3 c/s (delta response), the significance of this as an isolated phenomenon is not clear, since no definite, infallible relationship has yet been observed between any single factor or group of factors and the appearance of delta rhythms on over-breathing (Dawson and Greville, 1963).

Brill and Seidemann (1941) showed that 40% of normal children between 4 and 6 years of age developed 2-6 c/s waves on over-breathing. They concluded that such waves appearing on over-breathing cannot be considered as abnormal because of their high incidence, particularly in young children.

Gibbs, Gibbs, and Lennox (1943) demonstrated the appearance of large slow waves on over-breathing in 70% of normal children between 3 and 5 years of age, and in 50% between 6 and 10 years.

Since according to the literature many normal children are likely to develop such waves on over-breathing, we searched for an explanation in the subjects' history which may be correlated with this condition. Birth asphyxia can be considered as such, though clinical and EEG follow-up studies performed with matched controls are discordant (Atkinson, Fraser, Lowit, and Pampiglione, 1962; Dürrgl, Vukadinović, and Vujčić, 1965).

We investigated, therefore, children of the same age group, with a history of birth asphyxia, according to exact data of birth history, and matched controls.

METHODS

Twenty-nine premature children were chosen as subjects, all of whom had been born in the Schoepf-Merei Hospital for Premature Children. Of these, 16 had a record of birth asphyxia requiring revival procedures. One child born with a marginal placenta had to be classified in the asphyxiated group because of the long-term impairment of prenatal blood-circulation.

There were 12 children in the control group of non-asphyxiated children, and they were investigated in the same manner. The age of the children investigated was between 6 and 7 years. Weight limits were between 900 and 2,400 g.

The study was extended to investigation of the neurological and mental state of the children in addition to electroencephalography.

The EEG records were registered by an ink-writing E.C.E.M. apparatus working on either 8 or 16 channels. In each subject the resting record was followed by one taken during 4 min of over-breathing.

Not having a frequency analyser, the difference between resting patterns and that of over-breathing, was calculated, making use of the author's modification of the equation published by Széky and Csáki (1966): (see Appendix):

\[ I_a = \frac{S}{F} \]

where \( I_a \) is the 'index of activity,' \( S \) the area enclosed by the EEG curve and the isoelectric line, which quantity is proportional to the voltage, and \( F \) stands for the frequency.

In each subject the indices of activity were calculated for 5-sec periods sampled from the resting patterns, named \( I_{as} \) (Fig. 1, Column A), and that during over-breathing named \( I_{as} \) (Fig. 1, Column B). By dividing the activity index of over-breathing by the resting one, quotients of activity \( (Q_a) \) were obtained:

\[ Q_a = \frac{I_{as}}{I_{as}} \]

If slow waves failed to appear during over-breathing, the quotient was, evidently, close to unity. If, however, there was a delta response, which made the index of activity of over-breathing \( (I_{as}) \) to grow, then the quotient of activity was greater than unity.

In six children who showed the most elevated quotients of activity the procedure was repeated after the subjects were given 100 g glucose dissolved in 200 ml lemon-flavoured water. The patterns recorded were essentially identical with those registered before glucose administration. In the blood samples taken from the finger tips at the end of the over-breathing period, blood sugar levels of between 130 and 196 mg/100 ml. were found. Thus, hypoglycaemia could be ruled out of the factors eliciting delta response on over-breathing (Fig. 2).
RESULTS

Investigation of the neurological and mental state of the children gave normal results in all respects.

The values of the quotients of activities are tabulated (Table 1). Quotients of activity below 2-0 were considered as negative, those from 2-1 to 4-0 as slightly positive, while values above 4-1 were taken as markedly positive.

The listed data differ in two respects: (1) difference was found within the asphyxiated group itself, and (2) between the two groups.

1. The $Q_a$ values of the asphyxiated group range from 1-1 to 6-3. Three quotients are in the neighbourhood of unity (1-1, 1-3, and 1-4), respectively; in these and in two further subjects ($Q_a = 2-0$) there was actually no delta response to over-breathing. In the remaining cases positivity was in equal ratio either slight ($Q_a = 2-2$ to 3-5) or marked ($Q_a = 4-1$ to 6-3). So, positive values were according to mathematical statistical analysis significantly more frequent in the asphyxiated group.

2. Comparison of the $Q_a$ values of the two groups showed that even the highest activity quotients of the non-asphyxiated group ($Q_a = 2-4$ and 2-6) fell near the border of negativity and slight positivity.

Mathematical analysis of the difference between the two groups by Student’s two-sampled $t$ test was highly significant ($t = 3-52; P < 0-01$).

DISCUSSION

According to Morrice (1956) large slow waves appearing on over-breathing can be related to the following factors: age, rate and depth of ventilation, posture, oxygen content of the atmosphere, blood sugar, and hydrogen ion concentration of the blood. The author offers the addition of a seventh factor: the inherent stability of the subject. It is suggested that there is some intrinsic quality in an individual which determines his response to over-breathing and may outweigh the effect of factors already known. Examination of the known factors affecting the over-breathing response confirms the existence of a gross and individual variation.

In the two categories of children studied the first six factors mentioned above were kept constant. All the children were 6 to 7 years old. Over-breathing was performed under similar conditions, and the children inhaled atmospheric air. The posture was supine in every instance. Blood sugar determinations

![Fig. 1. EEG records of the 17 children born with anoxia, (16 with birth-asphyxia, and one with marginal placenta) arranged in the same order as they are shown on the Table. Column A shows the resting records, Column B after over-breathing. Calibrations 50 $\mu$V and 1 sec. Electrode positions are in each case the same on the resting records and on the ones after over-breathing: fronto-precentral.](http://jnnp.bmj.com/first-published-as-10.1136/jnnp.31.3.263-on-1-June-1968/downloaded-from)

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The serial numbers of the asphyxiated group are identical with those of Figure 1.

*Born with marginal placenta.
Birth asphyxia and delta response to over-breathing in non-epileptic children

in the children having the highest values of quotients of activity yielded levels in the range of alimentary hyperglycaemia, which according to Heppenstall (1944) excluded a hypoglycaemic origin of the delta response.

Blood pH estimations were omitted, since according to Davis and Wallace (1942) the comparison of the measured changes in pH and pCO₂ with changes in the EEG reveals no clear correlation, and the subject tended to have the greatest amount of delta waves when the measured changes in pH and pCO₂ were the least. Moreover, Engel, Ferris, Stevens, Logan, and Webb found that the significant changes in blood pH and carbon dioxide content resulting from over-breathing took place during the first minute and seemed to be of much the same order in everyone; yet, the effect on over-breathing varied greatly from person to person.

The factors described in the literature as determining the actual condition of the subject investigated at a given time do not explain the significant differences among the individual EEG changes observed. If, however, the children are classified according to birth history into two distinct categories, asphyxiated and non-asphyxiated, then the quotients of activity—that is, the appearance of large slow waves on over-breathing—will be found significantly more raised in the asphyxiated group. Consequently, we have not to do in our cases with any 'inherent stability' or 'intrinsic quality', but with asphyxia taking place at birth, leading even after a lapse of 6 to 7 years to the appearance of large slow waves on over-breathing.

In this respect, two further questions may be asked: (1) Supposing that the delta response to over-breathing is a late consequence of birth asphy-
xia, why does it not appear in every subject asphyxiated at birth? (2) How can this response be elicited several years after the existence of asphyxia at birth without other pathological signs, even in the resting EEG pattern?

1. In the present series there were three children with quotients of activity close to unity in the asphyxiated group—that is, children having birth asphyxia without delta response to over-breathing. The incidence of persons with delta response to over-breathing decreases rapidly with increasing years, according to the studies of Brill and Seidemann (1941) and of Gibbs et al. (1943). We do not know, therefore, whether these children had this response before the investigation. The maximum incidence of delta response to over-breathing in the 3-to-5 year and the 4-to-6 year age group, respectively, can be explained, perhaps, by the fact that children under 3 years cannot perform satisfactory over-breathing. (A further study in preparation deals with the age group under 3 years and applies a special technique to elicit the delta response in question.)

2. The second problem is closely connected with the pathogenesis of delta response to over-breathing. Space restricts detailed discussion of the question, so we allude simply to the most frequently mentioned theories of the literature. Gibbs, Gibbs, Lennox, and Nims (1942) suggest that inadequate compensatory vasoconstriction is unable to prevent a fall in carbon dioxide content in the brain, so producing delta response to over-breathing (hypocapnia theory), whereas Davis and Wallace (1942) claim that cerebral hypoxia brought about by vasoconstriction may be the immediate cause (hypoxia theory).

However, Clark, Misrahy, and Fox (1958) using chronically implanted polarographic electrodes showed that hyperventilation of the cat with air through a tracheal cannula causes a fall in mean Qa content of the brain substance. So it could be proved experimentally that hyperventilation produces at all events hypoxia of the brain.

There is no doubt that cerebral hypoxia can elicit large slow waves in the EEG pattern even without over-breathing, first demonstrated by Berger (1934) and by Gibbs, Davis, and Lennox (1935), and treated abundantly in the literature since then (Meyer and Gastaut, 1961).

Preswick, Reivich, and Hill (1965) stated, however, in a study of normal adults that only the combined technique (over-breathing followed by hypoxia) proved to be consistently reliable in eliciting delta response. The effectiveness of the combined technique was considerably greater than that of either over-breathing or hypoxia alone.

As mentioned above, marked positivity (Qa = 4.1 to 6.3) was seen only in members of the asphyxiated group. It must be presumed that the pathogenetic factor eliciting delta response to over-breathing is related to previous asphyxia. An anoxic state present during birth would presumably 'sensitize' the brain to hypoxia with the result that the noxious agent (anoxia) would elicit the same response later at a lower threshold level. This presumption is supported by the findings of Preswick et al. (1965) that the combined technique induced delta rhythms in 100% of normal adult persons in the age group of 30 to 34 years. Thus, the appearance of delta response seems to be highly dependent on the intensity of the stimulus applied.

The 'gross and unexplained individual variation' of EEG changes due to over-breathing in normal subjects would be, therefore, the lowered threshold of hypoxia eliciting delta response to over-breathing. According to the significant difference between asphyxiated and non-asphyxiated groups of children, the diminution of the threshold would depend on the existence and severity of the anoxia at birth. The physio-pathological explanation of the differences of the threshold awaits subsequent studies.

Previous work substantiates the close connexion between EEG responses to over-breathing and epilepsy. Since the reports of Foerster (1924) and Rosett (1924) it is well known that epileptic seizures can be elicited by over-breathing. In 1934 Berger observed the effect of over-breathing on the EEG of an epileptic. Gibbs et al. (1935) stated that over-breathing which produced large slow waves in normal subjects also tended to precipitate seizures in epileptic persons.

Neither before nor during the over-breathing were the clinical or EEG phenomena of epilepsy observed in any of the children investigated by us. Yet, we agree with Brill and Seidemann (1941) that the EEG change to over-breathing is similar to the change in the spontaneous records or in those taken during over-breathing in epileptic patients. According to these authors it does seem to represent a tendency to the convulsive state which is gradually outgrown, and it is possible that the children whom continue to show the appearance of delta response to over-breathing are the ones from whom the adult epileptic population is derived. This presumption is consistent with our view about the EEG changes appearing on over-breathing observed in children having had asphyxia at birth.

SUMMARY

The origin of delta response to over-breathing is discussed. Sixteen children with a history of birth
asphyxia and 12 without it were investigated. One child having a birth history of marginal placenta was classified among the asphyxiated ones.

As a measure of the large slow waves elicited by over-breathing a mathematical formula is used ('index of activity'). From the ratio of the indices of activity before and during over-breathing characteristic quotients of activity can be calculated (Qa). It is regarded as a measure of the effect of over-breathing.

The mean of the Qa-values was significantly greater in the asphyxiated than in the non-asphyxiated group.

It is suggested that the delta response to over-breathing shown by normal subjects seems to be in our cases a late consequence of birth asphyxia. This appears to be responsible for the lowered threshold of cerebral hypoxia which may be manifested at a later age by delta response to over-breathing.

APPENDIX

The method of Székely and Csáki contains the following mathematical formula for the measurement of what the authors call 'synchronization index':

\[
I = \frac{T}{n \cdot s^2}
\]

where \( T \) = the approximation of the area enclosed by the EEG-curve and the isoelectric line,
\( n \) = the frequency,
\( s \) = the standard deviation of the intervals of the peaks of the curve, \( i.e. s^2 = \frac{\sum X}{n-1} - \frac{x^2}{n} \)
\( x \) = the intervals of the consecutive peaks of the curve,
\( \bar{x} \) = the algebraical average of the intervals.

REFERENCES


