ABNORMAL NEURONAL MIGRATION, DERANGED CEREBRAL CORTICAL ORGANIZATION, AND DIFFUSE WHITE MATTER ASTROCYTOSIS OF HUMAN FETAL BRAIN: A MAJOR EFFECT OF METHYLMERCURY POISONING IN UTERO*

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ABSTRACT

Detailed clinical and neuropathological studies have been made in two fullterm newborn human infants who were exposed to methylmercury in utero as a result of maternal ingestion of methylmercury-contaminated bread in early phases of pregnancy. High levels of mercury were detected in various regions of the brain at autopsy. Study of the brains revealed a disturbance in the development in both cases, consisting essentially of an incomplete or abnormal migration of neurons to the cerebellar and cerebral cortices, and deranged cortical organization of the cerebrum. There were numerous heterotopic neurons, both isolated and in groups, in the white matter of cerebrum and cerebellum and the laminar cortical pattern of the cerebrum was disturbed in many regions as was shown by the irregular groupings and the deranged alignment of cortical neurons. Prominent in the white matter of the cerebrum and the cerebellum was diffuse gemistocytic astrocytosis accompanied by an accumulation of mercury grains in their cytoplasm. These findings indicate a high degree of vulnerability of human fetal brain to maternal intoxication by methylmercury. A major effect appears to be related to faulty development and not to destructive focal neuronal damage as has been observed in mercury intoxication in adults and children exposed postnatally.

INTRODUCTION

A catastrophic outbreak of methylmercury poisoning occurred in Iraq during the winter of 1971 to 1972. In all, 6,530 patients were hospitalized and 459 died.

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The cause of the outbreak was consumption of homemade bread prepared from seed grain of wheat treated with methylmercury fungicide. Approximately half of the patients were female and a substantial number of them were of childbearing age. Many aspects of this outbreak have been studied and published (3, 9).

Reported studies (1, 2, 4, 11) indicate that in man and in experimental animals methylmercury readily passes from mother to fetus, and once across the placenta it may have a greater affinity for the fetal central nervous system than that of adults (23, 33). It has been established from clinical studies that neurological damage can occur in human fetuses when exposed to methylmercury in utero (1, 2, 14, 17, 29) and that the fetus is more sensitive than the mother to the toxic effects of methylmercury (14). The clinical manifestations of affected infants include a variety of cerebral palsy syndromes encompassing mild to marked motor disorders and mental retardation. Publications on the abnormal changes in human fetal brain caused by maternal ingestion of methylmercury are limited to two cases from Minamata by Matsumoto et al. in 1965 (20).

In this report the pathological changes are described in the brain of two fullterm infants from the Iraq outbreak in 1971–1972. They were exposed to methylmercury in utero as a result of maternal ingestion of methylmercury-contaminated bread in the early stages of pregnancy.

REPORT OF CASES

Clinical Summaries

The first case was that of an infant born to a 28-year-old woman who began to consume methylmercury-contaminated bread 3 or 4 times daily for about 10 weeks when she was approximately 6 to 8 weeks pregnant.¹

One or two months after beginning to consume methylmercury-contaminated bread, this woman began to experience malaise, severe abdominal pain, tongue and perioral numbness, numbness of the hands and feet and blurring of vision. A few weeks thereafter she developed shoulder and knee joint pains. When admitted to the hospital during her 6th month of pregnancy she was noted to have moderately slurred speech, decreased visual acuity, decreased peripheral visual fields, diminished sensation of the hands and the feet, and exaggerated deep tendon reflexes in all four extremities. Following hospitalization her symptoms and signs gradually improved. Except for decreased peripheral visual fields and moderately increased deep tendon reflexes in all four extremities she appeared relatively normal when examined two years later.

A fullterm female baby was born after normal labor and vertex presentation. The Apgar score was 9. She had normal muscle tone, grasp, Moro, and tonic neck and sucking reflexes. No abnormalities were reported on neurological examination. There were no apparent congenital malformations. The baby weighed 2,890 grams. Laboratory studies on the baby revealed a hemoglobin of 19.3%, a packed cell volume of 60% and a white count of 14,000/cu mm. The child was bottle-fed and appeared healthy initially. A week after birth she developed a fever of 38.4°C and vomiting and diarrhea. Examination of the cerebrospinal fluid at that time revealed a total protein of 65 mg%, chloride of 130 mEq/liter and glucose of 45 mg%. After vigorous antibiotic

¹ This infant-mother pair was included in a previous clinical report "Perinatal Methylmercury Poisoning in Iraq" by Amin-Zaki et al. in 1976 (2). Although some of the clinical data were given in that publication there are additional data which are pertinent for this report, and are included here.
therapy she recovered clinically and looked well. On the 33rd day she died unexpectedly. The general postmortem examination disclosed interstitial pneumonitis bilaterally, which was presumed to be the immediate cause of death. Samples of blood were collected from the infant regularly from birth until death. The total mercury level of the blood varied from 442 ng/ml to 658 ng/ml. Infant and mother blood mercury levels are listed in Table I. Mercury concentrations in the infant’s blood were approximately 2½ times greater than those of the mother’s blood at all determination points. The total mercury clearance half-times from the mother’s blood and from the infant’s blood were estimated to be 58 days by least-square linear regression analysis of the data points.

The second infant was born to a 20-year-old woman who was admitted while in her 8th month of pregnancy. She began to consume methylmercury-contaminated bread 3 to 4 times daily when she was 8 to 10 weeks pregnant and this continued for about 10 weeks thereafter. Her symptoms started with malaise, dizziness, visual disturbances, and numbness and weakness of the limbs and tongue. Her condition steadily deteriorated to the extent that one month after the onset of symptoms she was unable to see or walk. Her physical examination upon admission revealed a pale woman with severe dysarthria and marked ataxia. Her sight was grossly impaired though there was some retention of vision. The optic discs were atrophic bilaterally; hearing seemed to be within normal limits. Muscle tone was normal and there was no apparent atrophy. Deep tendon reflexes were exaggerated in all four extremities and Babinski responses were present bilaterally. Somatic sensation was diminished in all four limbs and position sense was markedly diminished. The patient was treated with a course of penicillamine (1.0 gm daily) for 14 days. Intravenous Vitamin B6 were initiated during her hospital stay.

On admission the total blood mercury level was 1188 ng/ml and that of inorganic mercury was 74 ng/ml. Other laboratory studies revealed a hemoglobin of 5 gm%, a packed cell volume of 22% and a white count of 9200/cu mm. The platelet count was 150,000, and reticulocytes were 0.3%. The erythrocyte sedimentation rate was 27 mm, serum iron was 54 mg%, the BUN 22 mg% and creatinine 0.6 mg%. Serum protein was 62 gm% with a ratio of albumin to globulin of 3.0/3.2. Following treatment the patient’s anemia improved.

A full-term female infant weighing 3,178 gms was born after normal labor. There were no evident congenital malformations. The Apgar score was 8. Grasp, Moro and sucking reflexes were within normal limits. The neurological examination was reported to be normal. Because of the high mercury content of the blood at birth (1,568 ng/ml), an exchange transfusion was carried out within four hours after delivery. She was exchanged with 450 cc of Type O negative blood. During the exchange transfusions she developed pallor and bradycardia requiring resuscitation. Despite these measures, soon after completion of the exchange transfusion the infant expired. Death occurred seven hours after birth.

**Neuropathologic Findings**

At autopsy one-half of the brain was used for determination of mercury levels of various selected regions and the other half was fixed in 10% formalin for pathologic study. The regional mercury levels (total and inorganic) are listed in Table II. Both brains were smaller than normal and the estimated weight based on the material available was approximately 250 gms each.

**TABLE I**

<table>
<thead>
<tr>
<th>Mercury Content in Blood (ng/ml)</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Hg</td>
<td>Inorganic Hg</td>
</tr>
<tr>
<td>Mother</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>726</td>
<td>35</td>
</tr>
<tr>
<td>At delivery</td>
<td>193</td>
<td>14</td>
</tr>
<tr>
<td>Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At delivery</td>
<td>516</td>
<td>28</td>
</tr>
<tr>
<td>At autopsy</td>
<td>575</td>
<td>175</td>
</tr>
</tbody>
</table>
TABLE II
Mercury Content in Brain (µg/gm) of Infants

<table>
<thead>
<tr>
<th>Regions</th>
<th>Case 1</th>
<th></th>
<th>Case 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Hg</td>
<td>Inorganic Hg</td>
<td>Total Hg</td>
<td>Inorganic Hg</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>1.39</td>
<td>0.11</td>
<td>13.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>1.35</td>
<td>0.26</td>
<td>7.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>1.02</td>
<td>0.20</td>
<td>3.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>1.57</td>
<td>0.22</td>
<td>6.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Calcarine fissure</td>
<td>1.60</td>
<td>0.49</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>1.38</td>
<td>0.27</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.37</td>
<td>0.18</td>
<td>7.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Pons</td>
<td>1.38</td>
<td>0.50</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Medulla</td>
<td>2.13</td>
<td>0.80</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>1.27</td>
<td>0.27</td>
<td>3.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Optic chiasm</td>
<td>1.09</td>
<td>0.52</td>
<td>4.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>—</td>
<td>—</td>
<td>8.1</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Gross Examination

Case 1. As shown in Figure 1, the external configuration of the brain was slightly abnormal with an elongated anterior-posterior diameter. The frontal lobe was relatively short, and the gyri were somewhat more broad and flat than is usual. There were areas consisting of multiple narrow gyri with shallow intervening sulci on the lateral aspects of the parietal, temporal and occipital lobes. An olfactory bulb was present and the corpus callosum appeared normal. Except for an heterotopic island of grey matter in occipital lobe white matter, cross sections of the brain revealed no gross abnormality. There was a slight difference in thickness of grey matter of cerebral cortex from place to place but this was not considered abnormal. The cerebellum and the brain stem appeared normal.

Case 2. The external configuration of the brain was similar to that in the previous case, but abnormal features were slightly more prominent. Gyrus formation was simplified in many areas. The superior temporal gyrus was narrow compared to the large, broad middle temporal gyrus and contained only a few secondary sulci (Fig. 2). The frontal lobe was short, and there was incomplete opercularization. There were multiple narrow gyri separated by shallow sulci in the frontal, occipital and parietal lobes. The olfactory bulb was present and the corpus callosum was normal. The cerebellum appeared to be slightly smaller than is normal. Multiple coronal sections revealed a uniform thickness of the cortex with few sulci of normal depth. The basal ganglia, thalamus and brain stem were within normal limits grossly. The white matter of the cerebrum and cerebellum appeared to be slightly reduced in volume. The hippocampus was normally formed.

Microscopic Examination

Except for minor differences in the severity of involvement, the histopathologic findings in the two brains were remarkably similar; they will therefore be described together. The findings consisted of very great numbers of heterotopic neurons in the white matter of the cerebrum and cerebellum and disturbances in the alignment and organization of neurons in the cerebral cortex. The stains utilized included hematoxylin-eosin, Luxol Fast Blue-cresyl violet, phosphotungstic acid hematoxylin (PTAH), Bodian, Lapchak's phosphine fast green, lipofuscin, periodic acid-Schiff reaction, trichrome and Sudan Black B stains. Details of the changes were as follows:

There were scattered foci of heterotopic grey matter within the leptomeninges in the deeper portions of the sulci. These foci contained both neurons and glial cells (Fig. 5). The molecular layer of the cerebrum contained many scattered pyramidal-shaped neurons some of which may represent persistent Cajal-Reitzius cells (Fig. 6). In many areas, various layers of the cerebral cortex exhibited an undulating irregular pattern (Figs. 3, 7). The cortical surface at these sites was smooth and free of gyri. In other areas the usual laminar pattern of the cerebral cortex was replaced by an irregular grouping or vertical alignment of neurons in all layers (Figs. 4, 7). Layer
Fig. 1. Gross photograph of the brain of Case 1. Note elongation of anterior-posterior diameter, short frontal lobe and irregular pattern of gyri and sulci.

Fig. 2. Gross photograph of the brain of Case 2. Note simplified gyral pattern. The frontal lobe is short and opercularization is incomplete. The superior temporal gyrus is narrower than the middle temporal gyrus.

II of the cerebral cortex contained many unusually large neurons. In all layers neurons were often encountered which were not aligned perpendicular to the pial surface; their apical dendrites pointed upward at various angles to the perpendicular (Fig. 4). The deeper layers were not distinctly defined and gradually blended into the white matter where there were large numbers of large pyramidal-shaped heterotopic neurons diffusely scattered as single neurons (Figs. 9, 10) or occurring in groups. They occurred in greatest numbers in the depths of the cerebral white matter but were also found in convolutional white matter. Noted deep in the white matter were groups of small, round, dark immature neurons (Fig. 8). In contrast to the severe abnormalities in the

FIG. 4. Photomicrograph of the outer layers of the cerebral cortex demonstrating irregular clusters of neurons with apical dendrites (arrows) pointing in different directions. Layer II contains many large pyramidal neurons. Case 2. Hematoxylin and eosin stain. Original Mag., × 100.
cerebral cortex and white matter, the deeper nuclear structures of the basal ganglia and thalamus were normal. The architecture and the individual neurons in the hippocampus were normal.

The general architecture of the cerebellum at the microscopic level was normal. There were large numbers of heterotopic neurons in the folial and medullary white matter throughout the cerebellum (Figs. 11–15), however, both single and in groups. Many were large pyramidal-shaped neurons, presumably Purkinje cells, particularly in the white matter of the folia. Small granule cells were mixed in heterotopic nests with larger pyramidal neurons (Fig. 11). The external granular layer was several cell layers in thickness and appeared to be normal. The deep cerebellar nuclei were intact and the brain stem was normal at all levels.
An additional prominent feature in the white matter of both cerebrum and cerebellum was the presence of numerous gemistocytic astrocytes containing large amounts of eosinophilic cytoplasm and irregular-shaped nuclei (Fig. 10). Fibers arising from these astrocytes were readily demonstrated by PTAH staining in both cases. These astrocytes were not associated with either reactive pleomorphic microglia or macrophages. Axons in the white matter were plentiful as visualized in the Bodian preparations. On the other hand glial elements in the white matter that could be identified as myelin-forming glia or as adult oligodendroglial cells were much less numerous than astrocytes except in a few cerebellar folia in Case 1, where myelin formation was evident.

**Photoemulsion histochemical procedure for demonstration of mercury in sections**

Representative sections from cerebrum and cerebellum were deparaffinized, dipped in Ilford photographic emulsion (K-2) and exposed in light-tight boxes for 1 day to 2 weeks at 4°C. Sections were then developed in Dektol and stained with hematoxylin and eosin. This technic has been used by a number of investigators (12, 21, 23, 27) for demonstration of mercury in tissues or cells. The procedure is identical to the method of emulsion-dipping radioautography, but the nature of the reaction which takes place is unknown. It is believed that the grains produced at the site of mercury represent a mercury-silver amalgam. This amalgam develops at the interface of the emulsion and cut cells along the top surface of the microscopic section, where intracytoplasmic mercury is directly exposed to the emulsion.

With this technic several grains of mercury were visualized in the perinuclear cytoplasm of many of the gemistocytic astrocytes (at least 3 grains or more per cell were required to be considered positive). Astrocytes containing grains were diffusely and randomly scattered in the white matter of the cerebrum and cerebellum of both cases (Fig. 10). It was of interest that only very rarely were mercury grains encountered in neurons either in the cortex or heterotopically situated. Control slides from autopsied brains from infants of similar ages not known to have been exposed to mercury were free of mercury grains. These control brains included one from a normal infant and two from infants with many gemistocytic astrocytes in the white matter unrelated to methylmercury poisoning.
DISCUSSION

The principal neuropathologic findings in the brains of these two infants were widespread neuronal heterotopias in the cerebral and cerebellar white matter, and abnormal patterns of organization and distorted alignment of neurons in the cerebral cortex. Although there were variations in the severity of the involvement in different regions, the abnormalities were the same. Focal nerve cell destruction in the cerebrum and cerebellum such as is typically seen in adult cases of methylmercury poisoning and in infants and children exposed postnatally was not encountered.

Pathologic changes of this nature are the outcome of disturbances in the development of the brain, more specifically, abnormal neuronal migration and derangement in the fundamental structuring of grey matter. Heterotopia and heterotaxia of neurons and disordered cortical organization are to be sure seen in a variety of conditions in man (5, 6, 10, 13, 22, 24, 31, 32) and in a number of experimental disorders (7, 15, 18, 34). They are therefore nonspecific changes. We believe there is strong presumptive evidence, however, for implicating methylmercury as the causal agent in these cases.

In the first place, the blood levels of mercury in both infants at birth were, markedly above the adult maximum toxic levels for man (200 ng/ml of blood) (19). Similarly, the tissue mercury levels in the brains following death (Table II) were strikingly above the levels of 0.1 to 0.4 μg/gm of tissue reported in normal infants in the area of Minamata, Japan (30).

![Fig. 10. Photomicrograph showing heterotopic neuron (arrow) and gemistocytic astrocyte (arrow head) in the white matter of the cerebrum. Case 2. Hematoxylin and eosin stain. Original Mag., × 200. Inset depicts an astrocyte with granules of mercury (white arrow) in the cytoplasm as seen by photoemulsion histochemistry. Case 2. Hematoxylin and eosin stain. Original Mag., × 1000.](http://jnen.oxfordjournals.org/)
Secondly, exposure to toxic amounts of methylmercury first occurred during the critical period of neuronal migration [which normally begins at about 7 weeks gestation and continues into the third trimester (26)] in both infants. Evidence to support this statement is based on the following: a) It was possible to obtain a reliable clinical history from both mothers concerning the time of onset and duration of exposure to methylmercury as a consequence of ingestion of contaminated bread; b) the blood levels of mercury in both mothers when hospitalized during pregnancy were at toxic level for adults, and it has been established that fetal blood levels are generally 2½ times higher than maternal levels (2); and c) in Case 1 it was possible to determine mercury levels in serial segments of hair samples of the mother permitting a retrospective tracing of mercury levels as far back as 7½ months prior to the ingestion of the methylmercury-contaminated bread. The mercury content of the hair in this mother rose rapidly at the beginning of the ingestion of the contaminated bread and reached a maximum level of 400 μg/gm of hair at the 6th month of pregnancy. It is known from the studies of Skerfving (28) that a fairly constant ratio of mercury in hair to that in blood is maintained, the average ratio being 250. The calculated ratio based on multiple analyses in this case was approximately 300 (the data on this mother’s hair analysis are reported in detail in reference 2). Assuming that the fetus had a somewhat higher blood mercury level than the mother, it can be estimated that the maximum blood level during the second trimester in this infant may have been as high as 2000 ng/ml.

Another aspect suggesting a link to methylmercury poisoning in these cases is the striking similarity of the gross and microscopic changes in the two brains. Furthermore, although Matsumoto et al. (20) did not emphasize developmental changes in their report of the autopsy findings in two cases exposed to methylmercury prenatally, they described developmental features of the same nature as those in our cases.

It is important to note that in our cases there were no focal neuronal destructive changes in the cerebrum and cerebellum such as are typically seen in adult cases or in infants and children exposed postnatally to methylmercury. On the other hand, the large numbers of gemistocytic astrocytes in the cerebral and cerebellar white matter must be accepted as indicative of a reactive phenomenon to some type of destructive process. The nature of this white matter insult, its time of occurrence and its significance remains obscure. In Case 1, which survived 33 days after birth, a disorder in the white matter might be thought to reflect some insult acquired around the time of birth. This would

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Fig. 11. Photomicrograph of cerebellum showing numerous small granular neurons (arrow) and scattered large pyramidal neurons (arrow heads) in the white matter (WM). Case 1. Hematoxylin and eosin stain. Original Mag., × 40.

Fig. 12. Photomicrograph of heterotopic Purkinje cells (arrows) in cerebellum. One is deep in the white matter, one at the lower margin and one in the middle of the granule cell layer. Case 1. Luxol Fast Blue-cresyl violet (LFB-CV) stain. Original Mag., × 100.

Fig. 13. Photomicrograph of cerebellum demonstrating several groups (arrow) of large pyramidal neurons in the white matter. Case 2. Hematoxylin and eosin stain. Original Mag., × 25.

Fig. 14. Photomicrograph of cerebellum showing scattered heterotopic Purkinje cells in the white matter and sparsely populated internal granular layer. E: External granular layer. P: Purkinje cell layer. I: Internal granular layer. Case 1. LFB-CV stain. Original Mag., × 100.
Fig. 15. Photomicrograph of cerebellum. There are numerous clumps of heterotopic Purkinje cells (P) and small granule cells (g) in the white matter. LM: Leptomeninges. E: External granular layer. P: Purkinje cell layer. I: Internal granular layer. Case 2. Hematoxylin and eosin stain. Original Mag., × 25.
be excluded in Case 2, however, since her survival was for only seven hours and the astrocytic response was probably at least several weeks old on the basis of the extent of production of glial fibers. Although there were definitely fewer numbers of myelin-forming glia and adult forms of oligodendrocytes than astrocytes in the cerebral and cerebellar white matter in both cases, and myelin had begun to develop in only a few cerebellar folia in Case 1, there was no frank necrosis nor were macrophages present in either case. In addition, axons in the white matter were not remarkable. Thus in both cases the gemistocytic astrocytosis seems to represent a response which is rather disproportionate in degree to the amount of tissue destruction, and probably indicates a long-standing reaction. We feel it is also noteworthy that the astrocytes had the same generalized cerebral and cerebellar white matter distribution as the widespread neuronal heterotopias, and many of them contained mercury grains as demonstrated by the photoemulsion histochemical procedure. With these features in mind we believe that it is possible that methylmercury might have caused or at least contributed to the production of the astrocytic response. There are of course other causes of prenatal white matter degeneration, and one cannot exclude the possibility that the intracellular mercury demonstrated by the photoemulsion histochemical procedure simply represents non-specific phagocytosis by astrocytes.

Nonetheless, taking into account all of the histopathological and toxicological findings in our two cases, the possibility that the manifestations of disturbed neuronal migration and the exuberant white matter astrocytic reaction were both caused by methylmercury merits serious consideration. Disturbances in the normal growth and development of neurons and astroglia, particularly the intimate neuronal-glial relationship that exists during neuronal migration, might well represent the fundamental problem underlying the complex pathological changes encountered in these infants. This hypothesis is particularly attractive since there is now evidence that astroglia are present much earlier than formerly believed, i.e., at least as early as the 8th to 10th week of gestation (8).

The two cases of prenatal exposure reported here stand in sharp contrast to the two autopsied cases reported by Matsumoto et al. (20). They found widespread focal neuronal destruction, and in their view the basic pathological changes in fetal methylmercury intoxication were essentially the same as those described in adults or in children exposed postnatally (16, 30). As previously mentioned, however, Matsumoto et al. also observed developmental changes in their cases, and noted that these features constituted a point of difference from the adult disease, though they discounted the importance of these developmental findings. Whether or not other contributing factors (such as anoxia) might have influenced the final outcome of the pathological changes seen in their cases remains uncertain. The children they examined postmortem had survived for 6 years, 3 months and 2 years, 6 months, respectively, with repeated convulsive seizures during life. Our cases died shortly after birth.

If our hypothesis is correct that the major effects of methylmercury poisoning in utero are aberrant neuronal migration and faulty cortical organization,
then this places methylmercury in an entirely new perspective with respect to its toxic effects on growing fetal brain. Experiments are in progress in animals to test this hypothesis.

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