Levels of mercury and pathological changes in patients with organomercury poisoning

T. AL-SALEEM [a] & THE CLINICAL COMMITTEE ON MERCURY POISONING [b]

Autopsies were carried out on 4 adults who died during the outbreak of mercury poisoning in Iraq and on 4 infants who were exposed to organomercury in utero. Mercury levels in tissues and in some body fluids were determined. The high levels of mercury in the central nervous system and the marked neuronal degeneration are noted.

Aspects of the outbreak of methylmercury poisoning in farmers and their families in Iraq in 1972 were described in detail by Bakir et al.[1] In this paper we describe the pathological findings and mercury levels in the tissues of 8 patients autopsied between March and June 1972. All patients or their pregnant mothers were known to have consumed bread prepared from seed wheat treated with methylmercurial fungicide.

METHOD

The patients included 4 infants - 2 stillborn identical twins (B15 and B16), a newborn (B21) who lived 12 hours only and died during an exchange transfusion, and a fourth infant, 6 weeks old (B18) who died suddenly in bed. The 4 adults were the mother of the stillborn twins, who died a few hours after delivery (MC61), a boy 17 years old (MC3), a man 35 years old (A36), and a woman 32 years old (A37). All adults had severe neurological manifestations.

Blood and body fluids obtained during autopsy, and fresh tissues, were taken for the estimation of the levels of mercury by the flameless atomic absorption method. Tissues were fixed in 10% buffered formaldehyde solution.

RESULTS

Total and inorganic mercury levels in body fluids are shown in Table 1; those in tissues are shown in Table 2.

[a] Department of Pathology, College of Medicine, University of Baghdad, Baghdad, Iraq.

[b] Ministry of Health, Baghdad, Iraq. The members of the Clinical Committee are: Professor Salem F. Damluji (Chairman), Dr Mehdi Murtadha (Secretary), Dr Adbul-Hamid Al-Abbasi, Professor Laman Amin-Zaki, Professor Farhan Bakir, Dr Sami El-Hassani, Department of Medicine, College of Medicine, University of Baghdad; Dr Khaldoon Al-Janabi, Dr Khaldoon Al-Omar, Karama Hospital; Dr Jafar Kuwaiti, Al-Shaab Hospital; Dr Fuad Audeau, Kadhimain Hospital; Dr Muhammed Ali Majid, Medical City, Baghdad.

TABLE 1. MERCURY LEVELS, TOTAL (INORGANIC) IN ng/nl, IN BODY FLUIDS IN 8 AUTOPSIED PATIENTS

Body fluid	Patient							
	B15	B16	MC61	B18	B21	MC3	A36	A37
Blood (ante mortem)	-	-	4455(192)	-	1860(142)	2221(136)	-	-
Blood (post mortem)	5964(552)	-	-	575(175)	1505(84)	2320(186)	4000(417)	1400(12)
Urine (post mortem)	-	-	-	-	-	-	820(288)	-
Bile (post mortem)	-	-	-	450(215)	-	1965(1325)	1340(288)	-
Cerebrospinal fluid (post mortem)	-	-	-	-	-	175(81)	-	-
Vitreous (post mortem)	-	-	-	-	142(39)	73(36)	-	-
Pericardiac fluid	-	-	-	-	129(26)	-	-	-

TABLE 2. MERCURY LEVELS, TOTAL (INORGANIC), IN ng/g, IN CENTRAL NERVOUS SYSTEM AND OTHER TISSUES OF 8 AUTOPSIED PATIENTS

Tissue	Patient							
	B15	B16	MC61	B18	B21	MC3	A36	A37
Brain (general)	24.5(1.1)	-	-	-	-	18.3(8.3)	34.8(2.3)	29.2(1.4)
Grey matter	56.2(2.3)	-	-	-	-	34.2(11.8)	80.0(20.4)	-
White matter	-	-	-	-	-	10.8(3.7)	-	-
Frontal lobe	21.8(1.8)	30.4(2.6)	-	1.4(0.1)	-	99.7(6.7)	13.3(4.5)	-
Parietal lobe	13.8(1.6)	38.0(5.1)	22.7(5.1)	1.0(0.2)	3.7(1.4)	8.7(4.4)	15.1(7.6)	-
Occipital lobe	21.3(1.6)	18.9(1.4)	28.0(6.7)	1.6(0.2)	-	-	-	-
Pons	-	-	-	1.4(0.5)	-	-	27.2(0.8)	-
Medulla	-	-	19.3(3.6)	2.1(0.8)	-	6.3(1.6)	11.4(1.6)	-
Cerebellum	-	25.4(2.1)	25.0(5.9)	1.7(0.4)	-	11.1(6.5)	16.7(10.3)	-
Calcarine fissure	-	-	-	1.6(0.5)	-	7.6(4.0)	-	-
Basal ganglia	-	11.5(2.1)	20.3(3.9)	1.4(0.3)	-	7.5(4.3)	19.0(5.8)	-
Spinal cord	-	28.4(4.2)	-	1.3(0.3)	3.5(1.8)	3.7(0.4)	-	-
Liver	31.2(3.5)	25.0(3.7)	26.6(9.9)	4.2(1.8)	-	21.2(11.2)	22.0(6.5)	78.0(22.0)
Kidney	14.3(0.7)	-	18.0(3.3)	2.4(1.3)	-	40.9(39.8)	40.9(39.0)	13.3(5.1)
Skin	-	16.2(0.9)	-	0.4(0.1)	-	2.3(0.4)	-	-
Muscle	-	21.4(3.4)	-	1.3(0.3)	-	3.7(0.7)	21.2(2.5)	-
Ovary	-	-	-	-	3.0(2.7)	-	11.0(10.0)	-
Testis	-	-	-	-	-	1.9(0.3)	-	-

As expected, the most remarkable changes were seen in the central nervous system. In the stillborn infants (B15, B16), delivered in April and supposedly exposed to their mother's high blood level of mercury (1455 ng/ml) for 5-6 months, the nerve cells were either poorly developed or totally absent, being replaced by an astrocytic and, to some extent, microglial proliferation. However, no gross congenital anomalies were observed. In the other infants exposed to their mothers' blood levels, which were lower (922 ng/ml for B21 and 481 ng/ml for B18), there were slight to moderate degenerative changes in the nerve cells.

In the 4 adults, the brains were normal in weight in 3 cases; in the fourth patient (MC3) who died about 6 weeks after the others, the brain was atrophic (900 g). There was convolutional atrophy, particularly in the occipital lobes.

In all cases, the leptomeninges were turbid and case MC3 also showed organized haemorrhages. On sectioning, there were many small foci of cystic degeneration, more prominent in the grey matter and basal ganglia.

Microscopically, the main feature was degeneration or complete loss of neurones. There was marked hypertrophy and hyperplasia of astrocytes. All layers of the cortex were involved to some extent, including the cerebellar cortex. Purkinje, basket, and stellate cells were severely affected, with a variable loss of granule neurones. In some cases, Purkinje cells were spared but showed unusual changes. Dr Lowell Lapham feels that the coarse thickening of the nuclear rim in many Purkinje cells is exceptional and does not recall seeing this feature in any other disorder (personal communication, 1973).

Outside the central nervous system, neuronal degeneration was also observed in the gastrointestinal tract. The liver showed fatty changes in most cases. In one case, there was tubular degeneration in the kidneys. In all 4 adults and the 6-weeks-old infant there was a confluent bronchopneumonia, which was considered the immediate cause of death.

DISCUSSION

Mercury levels in post-mortem blood may not be reliable. The high levels obtained in bile and urine and the low levels in other body fluids are shown in Table 1. The bile was obtained from the gall bladder and, evidently, the values depend on the degree of concentration taking place there.

The free placental transfer of mercury has already been reported by Bakir et al.[1] The tissue levels in the 2 stillborn infants (B15 and B16) and their mother (MC61) demonstrate a fairly comparable pattern of deposition in tissues. Since the mother died immediately after delivery, it can be presumed that she and the infants were exposed to the same amount of mercury and for the same period.

Takeuchi[2] reported tissue levels of mercury in patients suffering from Minamata disease. Klein et al.[3] reported an excellent experimental model of acute methylmercury intoxication in rats. Most of our patients were exposed to the methylmercury for a short period only and died some time after cessation of exposure. Certain points are worth notice and comparison. High levels of mercury were found in brain in this outbreak, even in the stillborn infants. In one patient autopsied later than the others (MC3), low levels were noted in the tissues other than the brain, liver and kidneys. In the last two organs, the high levels may be attributed to the inorganic mercury being excreted through them.

The distribution in the central nervous system seems to be relatively uniform. However, higher levels were observed in the grey matter. It is possible that variability in levels of the central nervous system may be due to the inclusion of different proportions of grey and white matter in randomly selected specimens. Further experimental evidence and more cases are needed to clarify this point.

The infants B18 and B21 were both exposed in utero to moderate levels of mercury in the maternal blood. B21 died 12 hours after it was delivered during an exchange transfusion. B18 died at 6 weeks of age from bronchopneumonia. In both cases, tissue levels were not very high, but in case B18 the levels were comparable to case 6 reported by Glomski & Brody[4] from Buffalo, NY. This indicates that the levels, at least in Glomski's case, were not normal and the neurological findings could have been due to mercurial exposure. The other 5 cases in his series have much lower levels that are probably "normal" for that area. Patient B21 had blood and tissue levels about 3 times as high as those of B18, but both had slight to moderate neuronal degeneration, in spite of the absence of clinical signs of disease of the central nervous system. It is hard to tell whether these patients died directly of mercury poisoning.

Our observations on the pathology of the central nervous system and the neuronal degeneration are similar to those reported by Takeuchi in Minamata disease[2] and by Klein et al.[3] in experimental animals. In the present series, the degenerative changes were patchy, involving various parts of the brain randomly and their severity was proportional to the levels of mercury in the blood and the duration of the disease.

The 4 infants had no congenital anomalies. However, histologically, almost complete absence of nerve cells was observed in the 2 stillborn infants exposed to a high maternal blood level of mercury. A similar result was produced experimentally by Murakami[5] and severe degenerative changes of the neurons were also reported by Nonaka[6] in rat embryos.

In summary, the marked neurotoxicity of organomercury seems to be dose-time dependent, rather nonselective and, when severe enough, involves almost every nerve cell in the body to some extent.

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RESUME

CONCENTRATION DES COMPOSES MERCURIELS ET MODIFICATIONS PATHOLOGIQUES CHEZ DES MALADES SOUFFRANT D'INTOXICATION ORGANOMERCURIELLE

On a autopsié 4 adultes décédés lors de l'épisode d'intoxication par les composés mercuriels en Irak et 4 nourrissons exposés in utero aux organomercuriels. La concentration de mercure dans les tissus et dans certains liquides organiques a été déterminée. On a noté des concentrations élevées de mercure dans le système nerveux central et une nette dégénérescence neuronale.

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