TISCIA 28, 57-62

A CONTRIBUTION TO THE STUDY OF THE CAUSE AND DISTRIBUTION OF MINAMATA DISEASE IN THE LOWER COURSE OF THE RIVER TISZA (YU)

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Karabasil, D. and Bukurov, D. (1994): A contribution to the study of the cause and distribution of Minamata disease in the lower course of the River Tisza (YU). -Tiscia 28, 57-62.

Abstract. The research was started after a mysterious disease had been observed with a ten-year-old girl in Novi Sad, Yugoslavia. It was manifested by convulsions lasting for several hours. These crises of consciousness repeated cyclically in irregular intervals of approx. 90 days. Diagnosis of the disease was Sindroma-Lenox-Gastaut.
Test on toxic metals shoved enormously increased mercury contents in the little patient's urine. Our further investigations brought us to the irrigation/drainage canal DTD (Danube-Tisza-Danube) a pond called Beljanska Bara and the river basin of the river Tisza. Fish from Beljanska Bara had a considerable quantity of accumulated mercury.
The child was poisoned postnatally in the phase of lactation through her mother, who had used the fish mentioned above regularly in her meals.
The goal of the paper is to prove that Sinrdoma Lenox-Gastaut is in fact postnatal poisoning with methyl-mercury in the phase of lactation.

Keywords: Phenyl-mercuric acetate, methylation, methyl-mercury, lactation, methyl-mercury poisoning, Sindroma Lenox Gastaut, DMPS.

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Introduction

Poisoning with mercury was known even in the Roman Empire. They believed that the verdict by which a slave was sentenced to a forced labour in mercury mines was in fact a death penalty. Mercury poisoning in the second half of the 20th century was very frequent spreading rapidly among many people like epidemic. One of the biggest and certainly the most notorious epidemic of this kind was observed in Japan, near Minamata Bay. The inhabitants of the bay were struck by a mysterious and serious disease. 121 persons were infected, and in the period from 1953 to 1966, 46 of them died. On the basis of investigations performed it was found out that they were infected with contaminated fish from the bay which was used as their food.

Contamination of fish with mercury reached to 50 mg/kg with some kinds, depending on the way of nutrition, size and other factors.

Mercury went to the bay through a polyvinyl factory Chisso Minamata which released this metal in its waste water. By the process of methylation in fish, mercury was transformed into its most toxic form: methyl-mercury.

The number of victims of this factory was later increased by more than approx. 100 persons who died after 1966, while more than 700 inhabitants of Minamata Bay suffered terrible physical and psychical deformations. The disease was named after this epidemic "minamata-disease".

Preliminary investigations

The investigations started with the case of ten-year-old girl who had first crises of consciousness when she was at the age of three.

The crises started with spasms of fingers usually of the left hand. The spasms were usually followed and replaced by tremor of fingers which was spread over the arm, from the arm it was expanded into the left side of the body, and finally came over the whole body. These crises of consciousness lasted for several hours before Valium i.v. was given after hospitalization. The crises occurred in irregular intervals of 3, 6 or 12 months, respectively. After comprehensive medical investigations, the final diagnosis was Sindroma Lenox-Gastaut. In the meantime the girl fell into a coma and came out of it after more than 60 days.

That mysterious disease was not observed and medical records were not found either with the girl's parents or ancestors. At the end of 1989, the research was focused on toxicology examinations. The child became the patient of Dr. med. habil. Max Daunderer toxicologist from Munich and she received the following treatment: For secreting of possible heavy metals from the body of the girl Dimaval was used produced by chemical-pharmaceutical factory Hely from Berlin. Active matter is 2,3-dimercapto-1-sodiumpropane sulphonate: (DMPS). This antidote had been synthesized by scientists and they achieved very good results with it in detoxification after poisoning with chloride of mercury. Here it was used mainly for detoxification of cumulated mercury (mostly organic).

Results of toxicological research

Analyses were based on urine samples and urinalysis. Urine I had been taken before antidote was inserted into the organism of the little patient. Urine II was always taken 60 minutes after inserting of antidote, while Urine III was taken 120 minutes after inserting of antidote into the organism.

Samples for the first analysis were taken on 12 February, 1990. The results of this analysis are presented in Table 1.

Table 1. Results of urine analysis on 12 February, 1990 before Dimaval treatment.

	Urine I	
	Obtained values	Normal values
Creatinine i.U	2,57 g/dm^3	
Mercury i.U.	15.4 μg/dm^3 6.0 μg/g creat	< 4
Zinc i.U.	958 μg/dm^3 373 μg/g creat	140 - 720 > 140

As it can be seen from Table 1 high values of excreted mercury point to the possible chronical poisoning with this metal.

Urine II and Urine III were taken 60 and 120 minutes, respectively, after inserting of 600 mg of Dimaval perorally.

From Table 2 it is obvious that in Urine III mercury was excreted in the quantity of 417.2 μg/g creat. As chronical poisoning appears already when more than 50 μg of mercury per g creatinine is excreted, it can be concluded that here in this case it is a very serious intoxication.

Table 2. Results of urine analysis on 12 February, 1990 after Dimaval treatment.

	Urine II 60 min. later		Urine III 120 min. later	
Element	Obtained values	Normal values	Obtained values	Normal values
Creatinine i.U.	1.59 g/dm^3	1.00-2.50		
Arsenic i.U.	3 μg/dm^3 2 μg/g creat.			
Lead i.U.	43 μg/dm^3 27 μg/g creat.			
Cadmium i.U.	1.2 μg/dm^3 2.0 μg/g creat.			
Copper i.U.	773 μg/dm^3 486 μg/g creat.	<500	1262 μg/dm^3 789 μg/g creat.	<500
Mercury i.U.	247.5 μg/dm^3 155.7 μg/g creat.	<50	667.5 μg/dm^3 417.2 μg/g creat.	<50

The next analysis of urine was performed on 26. February, 1990. Dimaval was given on 600 mg i.v. The obtained results are presented in Table 3:

Table 3. Results of urine analysis on 26 February, 1990 after Dimaval treatment.

	Urine II 60 min. later	
Element	Obtained values	Normal values
Creatinine i.U.	0.55 g/dm^3	1.00-2.50
Arsenic i.U.	6 μg/dm^3 11 μg/g creat.	
Lead i.U.	46 μg/dm^3 84 μg/g creat.	
Cadmium i.U.	0.3 μg/dm^3 0.5 μg/g creat.	
Copper i.U.	440 μg/dm^3 800 μg/g creat.	<500
Mercury i.U.	100.3 μg/dm^3 182.4 μg/g creat.	

From the above data it can be seen that mercury values excreted in urine were decreased to 182.4 μg/g creatinine. Between the two analyses the patient took one capsule of Dimaval (200 mg) every third day.

Table 4 presents the results obtained after 200 mg Dimaval was taken perorally on 5. March, 1990. Urine was taken 60 minutes after DMPS capsule had been taken.

In Table 5 analysis of urine performed on 2.

April, 1990. after taking Dimaval (200 mg) perorally is given. Urine was taken 60 minutes after taking Dimaval.

Table 4. Results of urine analysis on 5 March, 1990 after Dimaval treatment.

	Urine II 60 min. later	
Element	Obtained values	Normal values
Creatinine i.U.	1.16 g/dm^3	1.00-2.50
Arsenic i.U.	12 μg/dm^3 10 μg/g creat.	
Lead i.U.	39 μg/dm^3 34 μg/g creat.	
Cadmium i.U.	0.6 μg/dm^3 0.5 μg/g creat.	
Copper i.U.	658 μg/dm^3 567 μg/g creat. after DMPS	<500
Mercury i.U.	104.6 μg/dm^3 90.2 μg/g creat.	

Excretion of mercury was decreased, but it was still above the level of chronical poisoning, which is 16 μg/g creatinine, when 3 mg/kg of Dimaval is taken perorally.

Table 5. Results of urine analysis on 2 April, 1990 after Dimaval treatment.

	Urine II	
Element	Obtained values	Normal values
Creatinine i.U.	0.86 g/dm^3	1.00-2.50
Copper i.U.	236 μg/dm^3 274 μg/g creat. after DMPS	<500
Mercury i.U.	21.1 μg/dm^3 24.5 μg/g creat. after DMPS i.v. orally 10 mg/kg 3 mg/kg	<50 <50 <16

120 days after the beginning of the therapy, the urinalysis was performed on 16. July 1990, under the same conditions as the previous one (200 mg Dimaval perorally, urine taken 60 minutes later). At that time the patient took 200 mg of Dimaval weekly. The results of urinalysis to heavy metals are given in Table 6.

Excretion of mercury in urine at the level of chronical poisoning was found on 1. October, 1990. Urine sample was taken 60 min. after taking 200 mg of Dimaval that was a little more than 3 mg/kg of the weight of the patient. The obtained results are presented in Table 6.

The next analysis to heavy metals was performed on 28 January, 1991. Urine sample was taken 60 minutes after taking 200 mg of Dimaval. The results are given in Table 7.

From this Table it is obvious that total excreted mercury is 0.9 μg/g creatinine. It means that detoxification is finished. From the Table 7 it can also be seen that a greater part of excreted mercury is organic (0.7 μg/g creatinine).

Table 6. Results of urine analysis on 16 July, 1990 after Dimaval treatment.

	Urine II		
Element	16 July, 1990	01 Oct., 1990	Normal values
Creatinine i.U.	0.61 g/dm^3	2.14 g/dm^3	1.00-2.50
Lead i.U.	86 μg/dm^3 141 μg/g creat. after DMPS	230 μg/dm^3 107 μg/g creat.	<150
Cadmium i.U.	0.2 μg/dm^3 0.3 μg/g creat. after DMPS	1.1 μg/dm^3 0.5 μg/g creat.	<5
Copper i.U.	705 μg/dm^3 1156 μg/g creat. after DMPS	4200 μg/dm^3 1963 μg/g creat.	<500
Mercury i.U.	11.0 μg/dm^3 18.0 μg/g creat. after DMPS 3 mg/kg	34.3 μg/dm^3 16.0 μg/g creat.	<16
Selenium i.U.	8.3 μg/dm^3 13.6 μg/g creat.		
Tin i.U.	2.0 μg/dm^3 3.3 μg/g creat.		

Table 7. Results of urine analysis on 28 January, 1991 after Dimaval treatment.

	Urine II	
Element	Obtained values	Normal values
Creatinine i.U.	1.47 g/dm^3	1.00-2.50
Copper i.U.	460 μg/dm^3 307 μg/g creat. after DMPS	<500
Mercury i.U.	1.3 μg/dm^3 0.9 μg/g creat. after DMPS i.v. orally 10 mg/kg 3 mg/kg	<50 <50 <16
Organic Mercury i.U.	1.0 μg/dm^3 0.7 μg/g creat.	

The last toxicological analysis was performed on 1 August, 1991, under the same conditions as the previous ones. The results obtained are presented in Table 8.

Table 8. Toxicological analysis performed on 1 August, 1991.

	Urine II	
Element	Obtained values	Normal values
Creatinine i.U.	0.61 g/dm^3	1.00-2.50
Lead i.U.	53 μg/dm^3 87 μg/g creat. after DMPS	<150
Copper i.U.	1230 μg/dm^3 2016 μg/g creat. after DMPS	<500
Mercury i.U.	3.5 μg/dm^3 5.7 μg/g creat. after DMPS i.v. orally 10 mg/kg 3 mg/kg	<50 <50 <16

It is obvious from the above data, that this little patient suffered from serious poisoning with mercury. As the whole case started to resemble the poisoning in Minamata, Niigato, Alomogord, which were caused by poisoned fish or some other meat, our analysis was focused on the food the child was nourished for. Our investigations were focused mainly on fish.

In the course of our research, the patient's mother recalled that in the period of lactation, she used to eat a lot of fish.

Toxicological analysis on heavy metals was performed with mother on 12 March, 1990. Dimaval as antidote was given i.v. 600 mg. Analysis of Urine I before taking Dimaval is presented in Table 9.

Table 9. Toxicological analysis of mother's urine on 12 March, 1990, before Dimaval treatment.

	Urine I	
Element	Obtained values	Normal values
Creatinine i.U.	0.43 g/dm^3	1.00-2.50
Zinc i.U.	131 μg/dm^3 305 μg/g creat. after DMPS	150-720 >140

60 minutes after taking Dimaval, the sample of Urine II was taken. The results obtained are given in Table 10.

From Table 10 it is obvious that mercury content in urine of this patient is 397.2 μg/g creatinine, what is approximately the same to the content of mercury found with the child examined (Table 2).

Table 10. Toxicological analysis of mother's urine on 12 March, 1990, after Dimaval treatment.

	Urine II	
Element	Obtained values	Normal values
Creatinine i.U.	0.71 g/dm^3	1.00-2.50
Copper i.U.	1372 μg/dm^3 1932 μg/g creat. after DMPS	<500
Mercury i.U.	282.0 μg/dm^3 397.2 μg/g creat. after DMPS i.v.	<50

It was most likely that fish was the possible source of mercury.

Investigations on the source of mercury

Our analysis started with the very beginning - we examined all details from the child's birth - (the end of June, 1980). In the patient's family fish was regularly in meals (even 4 times a week). The patient's mother especially ate fish in the phase of lactation of the baby, at the end of August, in September, October, November and December. In 1980 the mother ate fish from a pond called Beljanska Bara, situated near the village Turija in the central part of Backa (in Vojvodina). By leafing through a list of the factories in this part of Backa, and analyzing which of them used mercury in their plants, we came by the factory "Agrobacka" from Backa Topola where fungicides on the basis of organic mercury are used for seed processing mainly phenyl-mercuric acetate in "Zorosan" and "Radosan". After moist treating of seed water solutions of phenyl-mercuric acetate flew through waste-water industrial sewage system into the little river Krivaja - which empties into the irrigation/drainage canal DTD near Turija. Beljanska Bara gets water from the canal 500 meters farther. This canal flows into the river Tisza near Becej.

Sampling

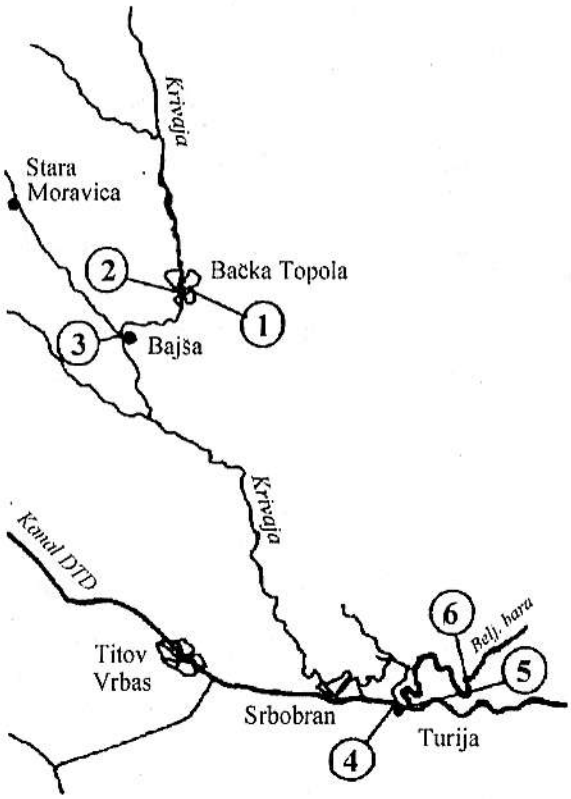

Fig. 1. Sampling places. 1, 2, 3, 4 and 5 - places where water and silt samples were taken, 6 - the place where fish samples were taken.

Samples of river silt were taken from the Krivaja river and sewage system of Backa Topola as shown in Fig. 1. These specimens were taken at the beginning of March, 1990, when all activities regarding treating seed with fungicides were finished a long time ago. The first sample was taken from industrial sewage system of the factory producing seed material; the second at the mouth of the Krivaja - where the sewage system flows into it, the third one at Bajsa (at the place where branches of the river Krivaja from Backa Topola and Stara Moravica join); the fourth sample was taken at the mouth of the Krivaja into DTD canal, branch Bezdan-Vrbas-Becej; and the last (the fifth) one was taken from Beljanska Bara - (from its mouth) - (Fig 1).

Samples of fish were taken at the beginning of January, 1990 from Beljanska Bara. At the time when the samples were taken, bigger fish individuals unfortunately could not be caught, although they would be much better and more representative for our research. Fish samples were taken from the most distant point of Beljanska Bara in relation to the irrigation/drainage canal DTD-as the source of pollution (from which water is obtained) - Fig. 1. Also these samples were taken when all activities regarding treating seed with fungicides were finished a long time ago.

Results

The results obtained regarding analysis of silt to the total mercury are presented in Table 11. A considerable amount of mercury was found in the last 3 samples of silt, sand with a little share of organic matter prevailed, what was probably one of the reasons for decreased quantity of mercury in these samples.

Table 11. Results of silt examination on total mercury.

Sampling place	Mercury content [mg/kg]
Sewage system of the factory producing seed material	0.56
Place where sewage system empties into the Krivaja, at Backa Topola	0.31
Place where branches of the River Krivaja from Backa Topola and Stara Moravica join - near Bajsa	0.08
At the mouth of the Krivaja into DTD canal	<0.001
At the mouth of Beljanska Bara	<0.001

The results of fish examination are presented in Table 12. As it can be seen from the Table only predatory fish *Perca fluviatilis* L. is at the level of maximum allowed concentration of 0.5 mg/kg mercury. As mercury in fish is mainly in a methyl form of 70 - 90 %, methyl-mercury content is approx. 0.4 mg/kg, what is also at the level of maximum concentration allowed. Results of examining fish to total mercury are given in Table 12.

Lack in mercury with *Abramis sapa* Pallas can explained by the way of its nutrition because it usually takes place in the upper and surface layers of water.

Table 12. Mercury content of fish species.

Fish species	weight [g]	Mercury content [mg/kg]
Perca fluviatilis L.	240	0.44
Carassius carassius L.	62	0.19
Carassius auratus gibelio Bloch	265	0.13
Abramis sapa Pallas	71	<0.001

However, in order to come to valid and exact conclusions of the degree of mercury contamination of this region of central Backa, it is necessary to perform investigations on a greater number of fish samples (according to different kinds of size, age, and number).

Unfortunately, because of the war in Yugoslavia and the sanctions of the international community this research has been stopped. The goal of this paper is to arouse interest of some researchers outside Yugoslavia whose countries are not burdened with the international sanctions to continue this research.

Conclusion

On the basis of the obtained results and data mentioned above, the following conclusions may be drawn:

1. The paper has proved that the little patient and her mother are the victims of mercury poisoning.

2. At the same time, it is obvious that fish with mercury content of 0.5 mg/kg must not be used for nutrition in the phase of lactation, although it is allowed in the majority of European countries.

3. Sindroma Gastaut-Lenox is in fact postnatal poisoning with methyl-mercury in the phase of lactation.

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