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Toxic Effects of Chronic Mercury Exposure on the Retinal Nerve Fiber Layer and Macular and Choroidal Thickness in Industrial Mercury Battery Workers

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Background: The aim of this study was to evaluate the toxic effects of mercury on retinal nerve fiber layer thickness (RNFLT), macular thickness (MT), and choroidal thickness (CT) by using spectral-domain optical coherence tomography (SD-OCT) in battery industry workers who had been chronically exposed to mercury.

Material/Methods: Battery factory workers (n=31) and healthy non-factory employee controls (n=15) participated in the study. Participants were divided into 3 groups: Group 1 (n=15) was factory workers who had worked for more than 5 years in a mercury battery factory; Group 2 (n=16) was factory worker who had worked for less than 5 years in a mercury battery factory; and Group 3 (n=15) was healthy non-employees. Systemic symptoms were recorded. Ophthalmic examination included best-corrected visual acuity test, color vision test, full ophthalmologic examination, and SD-OCT of the RNLF, macula, and choroid. To determine mercury exposure, venous blood samples were collected and mercury levels were assessed.

Results: In our study group the most common systemic symptoms were insomnia (67.7%) and fatigue (67.7%). There were no significant differences between Group 1 and Group 2, but there were significant differences between Group 3 and both Group 1 and Group 2 in best-corrected visual acuity values (1=2<3), color vision scores, blood mercury levels, and duration (mean ±SD, range) of mercury exposure(1>2>3). OCT values of RNFLTs, MTs, and CTs of all 3 groups were statistically different from each another (1<2<3).

Conclusions: SD-OCT can be useful for evaluating the toxic effects of chronic exposure to mercury.

MeSH Keywords: Mercury Poisoning, Nervous System • Retinal Ganglion Cells • Tomography, Optical Coherence

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Background

Mercury (Hg) is a hazardous environmental and industrial pollutant that induces severe alterations in the body tissues of both humans and animals [1,2]. It exists in several forms: inorganic mercury, which includes metallic mercury, mercury vapor, and mercurous or mercuric salts; and organic mercury, which includes compounds in which mercury is bonded to a structure containing carbon atoms (methyl, ethyl, phenyl, or similar groups) [3].

Human mercury exposures occur chiefly through inhalation of elemental mercury vapor via occupational or dental amalgam exposure, or through ingestion of mercury bonded to organic moieties (methyl, dimethyl, or ethyl mercury), primarily from seafood [3]. Inhaled elemental mercury vapor is especially easily absorbed through mucus membranes and the lung and is then transported to the rest of the body via the blood. It accumulates in the brain, thyroid, breasts, myocardium, liver, kidneys, and eyes, and may be associated with dysfunction of those organs [3,4].

In recent studies it has been shown that mercury accumulates in the lens, optic nerve, optic disc, retina pigment epithelium, and retina [5]. Ocular findings in patients with chronic exposure to mercury are: discoloration of the cornea and lens, tremor of the eyelids, disturbances of vision and of extraocular muscles, and in very young children a special manifestation of acrodynia that includes photophobia, conjunctivitis, and keratitis [6] can be found. In addition, chronic exposure to mercury may result in peripheral vision loss, followed by a more severe central vision loss [7,8].

In the medical literature there is no study investigating the toxic effects of mercury on the ocular system by using spectral-domain optical coherence tomography (SD-OCT). Therefore, this review was written to focus on the use of SD-OCT to evaluate the toxic effects of mercury on retinal nerve fiber layer thickness (RNFLT), macular thickness (MT), and choroidal thickness (CT) in battery industry workers who had been chronically exposed to mercury.

Material and Methods

Study

The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Ethics Committee (Meeting: 03.01.2011; Document No. 09). Written informed consents were obtained from all subjects prior to recruitment.

Subjects

Battery factory workers (n=31) and healthy non-factory employee control subjects (n=15) participated in the study. Participants were divided into 3 groups: Group 1 (n=15) was factory workers who had worked for more than 5 years in a mercury battery factory; Group 2 (n=16) was factory workers who had worked for less than 5 years in a mercury battery factory; and Group 3 (n=15) was healthy non-employees collected from patients who had been seen in our clinic.

At the beginning of the study, factory workers were interviewed about physical complaints possibly resulting from mercury exposure, which included: dyspnea, gingivitis, involuntary tremor in the eyelids-face-fingers and hands, anxiety, attention difficulties, forgetfulness, insomnia, fatigue, and headache. Individuals who were using drugs, vitamins, cigarettes, or alcohol were excluded from the study, as were those who had (or whose family members had) diabetes, hypertension, or ophthalmological pathologies. The control group was composed of a random selection of patients who had been seen at our clinic and who had lived in Istanbul for at least 5 years. All participants were given a best-corrected visual acuity (BCVA) test, color vision test, full ophthalmologic examination, and SD-OCT of RNLF, macula, and choroid. These tests were performed in the routine facilities of the institute and the technicians administering the test were unaware of the diagnosis or employment history of the patients. Color vision scores (CVS) were determined using Farnsworth-Munsell (FM) 100 testing, which was performed in a dark room with test materials viewed under standard light conditions [9]. Subjects used near vision correction, if needed, and were given 2 min to complete each of the 4 test boxes. The approximate distance from the subjects' eyes to the test materials was 30–50 cm. Total error score was calculated according to the manufacturer's recommendations, and the square root of the total error score was used in analyses. A high value reflects a defect of color vision.

For the purpose of statistical analysis, Snellen chart visual acuity was converted to the logarithm of the minimal angle of resolution (log MAR) value [10].

To determine mercury exposure, venous blood samples were collected from each participant and elemental mercury levels were determined.

SD-OCT

SD-OCT was performed through undilated pupils using RTVue version 4.0 (Optovue Corp., Fremont, CA) by the same 2 investigators. Only scans that reached signal strengths of ≥6, which indicates a high-quality scan, were accepted for analyses. The RNFL scan pattern completes circular scans in 0.15 s at a diameter of 3.45 mm, targeted around the optic nerve head. The instrument makes use of a retinal cross-line scanning pattern that includes a 1024 A scan, and consists of two 6-mm orthogonal lines. With an automatic reversal of the image, the chorioretinal interface becomes adjacent with zero delay. The

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Table 1. Clinical complaints of workers exposed to mercury.

Symptom	No. subjects	% (total no of subjects)
Dyspnea	12	38.7
Ginjivitis	14	45.1
Anxiety	16	51.6
Attention difficulties	18	58.0
Forgetfulness	8	25.8
Insomnia	21	67.7
Fatigue	21	67.7
Headache	9	29.0
Involuntary tremor ın the eyelids-face-fingers and hands	3	9.7

Table 2. Ophthalmological and hematological findings of study groups.

Group	BCVA (logMAR)	CVS	BML (µgr/100 ml)	Exposure (mo)	Thickness (µm)		
					RNFL	MT	CT
1	0.11±0.83	245.33±40.92	77.06±13.07	89.46±19.24	98.73±4.44	93.93±3.34	168.66±9.39
2	0.07±0.68	144.25±18.92	18.31±4.78	34.43±14.79	110.31±11.40	118.62±5.62	198.13±24.06
3	0.0±0.0	51.06±5.28	1.67±1.18	0.00±0.00	124.86±10.05	143.20±5.51	225.60±14.43
p	X2=18.06 *p*=0.000*	X2=40.04 *p*=0.000*	X2=40.16 *p*=0.000*	X2=40.61 *p*=0.000*	X2=28.02 *p*=0.000*	X2=40.06 *p*=0.000*	X2=28.79 *p*=0.000*

BCVA – best-corrected visual acuity; CVS – color vision scores; BML – blood mercury level; RNFL – retinal nevre fiber layer thickness; MT – macular thickness; CT – choroidal thickness; *p* – significance. * Statistically significant difference.

retinal cross-line scanning method consists of the mean of 32 patterns in 16 directions, with no eye tracking. After measuring the peripapillary RNFLT, average values were obtained for evaluation. Measurement of MT was performed in a 1-mm diameter circle within the central macula (fovea) for all measurements. The RTVue-100 has a 5 mm axial image resolution, with an imaging speed of 26 000 axial scans per second. Scans of low quality or blinks were not included. CTs were measured perpendicularly from the outer edge of the retinal pigment epithelium (RPE) to the choroid-sclera boundary at the fovea itself, 500 and 1000 mm nasal to the fovea, and 500 and 1000 mm temporal to the fovea. Two sets of measurements were averaged. Differences between readings of the masked physicians were determined to be within 10% of the mean.

Blood mercury level analysis

Venous blood samples for mercury analyses were collected from the battery factory workers and healthy non-employees. The samples were analyzed for mercury content by a modified method described by Einarson et al. [11]. Briefly, samples were digested with a mixture of HClO4 and HNO3 overnight at 68°C. Mercury was reduced and analyzed by cold vapor, flameless atomic absorption spectrometry.

Statistical analysis

Version 11.5 SPSS (SPSS Inc., Chicago, IL) software was used for statistical analyses. Kruskall-Wallis tests were applied. Following the Kruskall-Wallis test, the Mann-Whitney U-test was applied for post-hoc comparisons (least significant difference [LSD]). Probability values of $p<0.05$ were considered statistically significant.

Results

Frequently reported systemic symptoms in the 31 participant workers are shown in Table 1.

Ophthalmological examination revealed no conjunctival, corneal, lenticular, or retinal abnormalities in any participant.

Median ages (min-max) of subjects in Groups 1–3 were 21.90 (24–36), 23.13 (24–33), and 25.50 (21–35) years, respectively.

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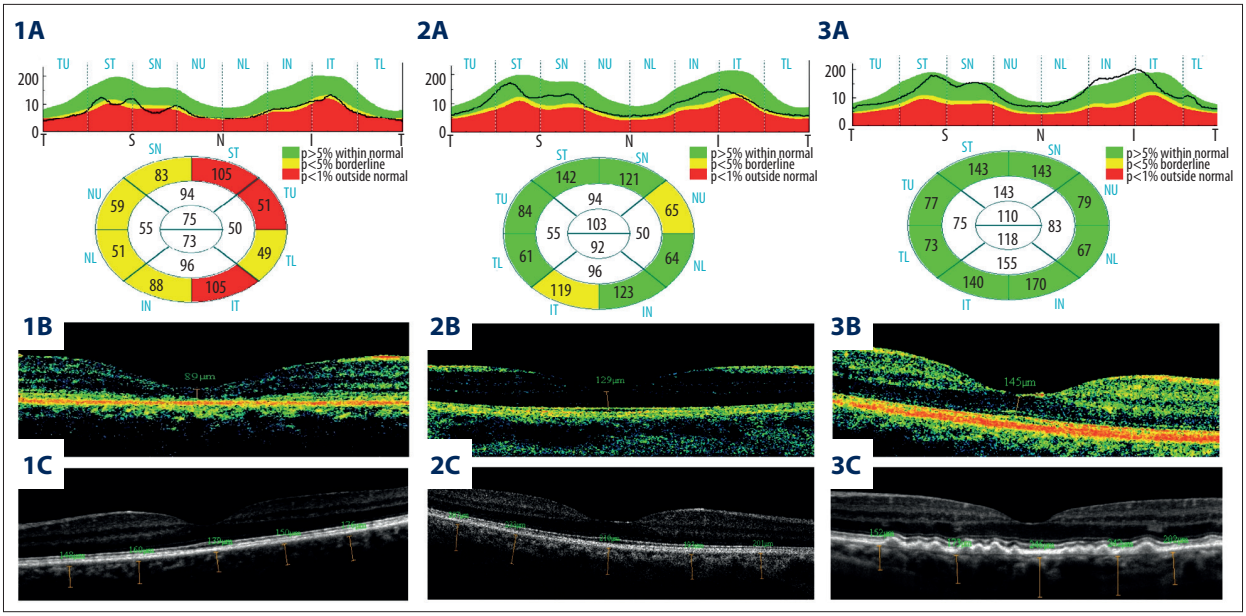

Figure 1. RNFL, macular and choroid thickness measurments by using optical coherence tomography. Group 1. **1A, 1B, 1C:** RNFL, macular and choroid thickness measurments of a patient in group 1. Group 2. **2A, 2B, 2C:** RNFL, macular and choroid thickness measurments of a patient in group 2. Group 3. **3A, 3B, 3C:** RNFL, macular and choroid thickness measurments of a patient in group 3.

Table 3. Correlation between BML and BCVA, CVS, RNFLT, MT and CT values.

	BCVA	CVS	RNFLT	MT	CT
BML	r=0.359	r=0.622	r=–0.410	r=–0.707	r=–0.522
	p=0.047	p=0.000	p=0.022	p=0.000	p=0.003

BCVA – best-corrected visual acuity; CVS – color vision scores; BML – blood mercury level; RNFL – retinal nerve fiber layer thickness; MT – Macular thickness; CT – choroidal thickness; *p* – significance.

There were no statistically significant differences in ages between groups (X^2=0.566, p=0.754). For all groups, BCVA (logMAR), CVS, blood mercury level (BML) (µgr/100 ml), duration of mercury exposure (months), OCT values of RNFLTs, MTs, and CTs (µm) are shown in Table 2.

There were no statistically significant differences between Group 1 and Group 2 (p=0.216), but there were statistically significant differences between Group 3 and both Group 1 and Group 2 with respect to BCVA values (1=2<3) (p=0.000), color vision scores (CVS), blood mercury levels (BML), and duration (mean ±SD, range) of mercury exposure (1>2>3) (p=0.000). The most observed color vision loss was in the blue-yellow range. OCT values of RNFLTs, MTs, and CTs of all 3 groups were significantly different from each another (1<2<3) (p=0.000) (Figure 1).

In addition, when the correlation analysis was performed, a negative correlation between BML and BCVA, CVS, RNFLT, MT, and CT was observed (Table 3).

Discussion

Our study demonstrates that there was a negative correlation between BML and BCVA, CVS, RNLFTs, MTs, and CTs. To the best of our knowledge, ours is the first study that investigated the relationships between BML and OCT findings.

Due to the absence of myelin sheath in retinal cell axons, the investigation of RNFL thickness by OCT allows visualizing the processes of neuroaxonal degeneration in different central nervous system disorders. In the literature there are some studies investigating the neuroaxonal degeneration by using OCT in schizophrenia, Parkinson disease, and Alzheimer disease [12–14].

Mercury is a hazardous environmental and industrial pollutant that has no known physiologic role in human metabolism and induces severe alterations in the body tissues of both humans and animals [15,16].

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Mercury has a high affinity for sulfhydryl groups, various enzymes and amino acids, N-acetyl cysteine (NAC), alpha lipoic acid (ALA), and glutathione (GSH), which provide about 10–50% of plasma protein antioxidant capacity [17,18]. It obstructs neurotransmission by acting as a strong competitive inhibitor of muscarinic cholinergic receptors [19]; inhibits the uptake of synaptic glutamate in neurons of the brain, resulting in an excitotoxic elevation of glutamate in the extracellular space and associated neuronal damage [20]; induces mitochondrial dysfunction and oxidative stress [21]; induces oxidative stress and cell cytotoxicity; and increases the secretion of amyloid, which may lead to neurodegenerative diseases such as Alzheimer and Parkinson diseases [22].

The major sources of mercury load in humans are food contamination, drug and vaccine preservatives, dental amalgams, and occupational exposure [23]. Following mercury exposure, decreased visual contrast sensitivity [24], impairment of scotopic (night) vision [8], reduced color vision and visual acuity [3], and in *in vivo* studies in laboratory animals vision loss [8] have been reported. Sabelaısh et al. [25] have reported visual disturbance, recurrent attacks of visual loss, visual field defects, absent or blunted corneal sensations, iris atrophy, and pallor of the optic disk in their patients after organomercury poisoning. In our study, we observed no significant significances between Group 1 and Group 2, but there was a statistically difference between Group 3 and both Group1 and Group 2 with respect to BCVA values (1=2<3). For CVS values, we observed significant differences between all groups (1>2>3). Although Feitosa-Santana et al. [26] and Ventura et al. [27] observed color vision loss in both chromatic systems (blue-yellow and red-green) in patients with chronic mercury vapor intoxication, Jedrejko et al. [28] and Cavalleri et al. [29] reported that the most observed color vision deficit was in blue-yellow range in workers exposed to elemental mercury vapor. In our study, the most observed color vision loss was in blue-yellow range, similar to results in the literature.

Accumulation of mercury in ocular tissues and ocular pathways may provoke anatomical and functional injuries to the eye.

After exposure to mercury, findings in the cornea, including loss of epithelium, necrosis of keratocytes, absence of inflammatory reaction, endothelial cellular swelling, endothelial increased vacuolization, and diminished intercellular junctions, can be observed [30,31]. In a study by Kairada et al., active accumulation of mercury in the lens was observed after exposure to mercury [32]. In their experimental study, Khavat and Dencker [33,34] found mercury in the receptor layers, pigment epithelium, and choroid in mice immediately killed after exposure. Additionally, Warfvinge et al. [4] observed mercury in choroidal and retinal pigment epithelium, in ganglion cell layers, and in the optic disc layer and optic nerve in squirrel monkeys after mercury exposure. Basu et al. [35] demonstrated that mercury decreases the number of NMDA receptors in several brain regions, including the basal ganglia, cerebellum, brainstem, and occipital cortex of mink. In addition, Sabelaısh et al. [25], in postmortem examination of a baby exposed to mercury and who was blind before death, observed the accumulation of mercury in the occipital lobe. According to the above-mentioned studies, it can be concluded that mercury has a toxic effect in the retinal photoreceptor layer, ganglion cell layer, optic disc, and optic nerve layer, and in the visual cortex layer. In our study, we found a negative correlation between BML and RNLFTs values.

However, Warfvinge et al. [4] reported in their experimental study on neural retinas that they did not find mercury in the retina of the squirrel monkey eyes after mercury vapor exposure. In another study, they declared that the photoreceptor layer contained no visualized mercury except in the foveal region in the squirrel monkey retina after in utero exposure to mercury vapor [5]. In our study we observed a negative correlation between BML and MTs. The values of MTs of all 3 groups were statistically different from each other (1<2<3). It can be speculated that if there is no mercury accumulation in the fovea, the MTs loss could be due to optic disc and optic nerve vasculitis, which occur after mercury exposure [5].

However, Warfvinge et al. [4] reported that after mercury exposure they did not observe mercury in choroidal vessel walls. In the literature there are associations between mercury toxicity and increased platelet aggregation [36], increased Factor VIII, reduced platelet endothelial cell formation and migration, decreased vascular endothelial repair, and decreased nitric oxide [37]. Additionally, the association between mercury toxicity and hypertension is well known [38–40]. It has been shown that choroidal blood flow is regulated by parasympathetic innervation, with fibers rich in the vasodilator's vasoactive intestinal polypeptide (VIP) and NO [41,42]. It has also been found that untreated systemic hypertension is associated with choroidopathy [43]. Under conditions such as decreased nitric oxide level and increased vasculopathy and choroidopathy, choroidal thickening may be an expected result. In our study, we observed a negative correlation between BML and CTs values. The values of CTs of all 3 groups were significantly different from each other (1<2<3).

In our study, BML of the healthy non-factory employees was detected as 1.67±1.18 µgr/100 ml. In our opinion this is due to industrial fossil fuel emissions and atmospheric mercury, including coal burning [44], which are responsible for mercury exposure, especially in industrial and crowded cities.

The weaknesses of our study include the facts that (i) the number of subjects was small, (ii) the visual field examination could not performed, (iii) urine should be collected over a 24-h period, and mercury levels were examined in urine instead of serum. It has been reported that urine samples are better for diagnosis of chronic intoxication [45] because of the

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short half-life of mercury in the blood, and (iv) we did not rule out the factors that may impair color vision, including chronic alcoholism, prolonged use of medicines (e.g., chloroquine), tuberculosis (e.g., ethambutol), and epilepsy (e.g., vigabatrin) [46].

Conclusions

We confirmed that chronic exposure to mercury has toxic effects on the retina, optic nerve neuronal fibers, and choroidal vasculature. In our opinion the reduced visual acuity is related to the accumulation and toxic effects of mercury in macula, retinal pigment epithelium, ganglion cell layers, and optic nerve neuronal fibers. It can also be related to optic disc and optic nerve vasculitis. Mercury toxicity should be considered as a problem of public health concern, and the harmful effects can be confirmed by SD-OCT. Further SD-OCT studies with larger numbers of subjects are necessary to confirm mercury toxicity in the RNFL, macula, and choroid.

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