Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2022;

Research Article / Araştırma Makalesi

The Assessment of Effect of Occupational Manganese Exposure on Cognition and Quantitative EEG Variables

Mesleki Mangan Maruziyetinin Kognisyon ve Kantitatif EEG Verileri Üzerine Etkisinin Değerlendirilmesi

[1]Tulin Akturk, [2]Gulay Celiker, [3]Mehmet Hamdi Sahan, [4]Gulsum Akdeniz, [5]Engin Tutkun,[6]Oktay Algin

[1]Kartal Dr. Lutfi Kırdar City Hospital, Department of Neurology, Istanbul, Turkey

[2]Ankara Occupational and Environmental Diseases Hospital, Department of Neurology, Ankara, Turkey

[3]Gaziantep University School of Medicine, Department of Radiology, Gaziantep, Turkey

[4]Ankara Yıldırım Beyazıt University School of Medicine, Department of Biophysic, Ankara, Turkey

[5]Yozgat Bozok University School of Medicine, Department of Public Health, Yozgat, Turkey

[6]Ankara Yıldırım Beyazıt University School of Medicine, Department of Radiology, Ankara, Turkey

Correspondence:
Tulin AKTURK
Kartal Dr. Lutfi Kırdar City Hospital, Department of Neurology, Istanbul, Turkey
e-mail: tulin_birlik@hotmail.com

Abstract

Occupational Mn exposure results in extrapyramidal system findings and cognitive impairment. We aimed to evaluate the effect of occupational exposure to Mn on cognition and quantitative EEG (qEEG) data in Mn exposed workers. One hundred seventy-five workers with occupational Mn exposure were included in this study. Pallidal index (PI) values were calculated in T1 weighted sequence of brain magnetic resonance imaging (MRI).The presence of T1 hyperintensity on MRI was evaluated by two independent neurologists. The serum, spot urine, and 24-hour urine samples were measuredMn levels. The total scores of MoCA test and sub-groups were determined. The qEEG measures were analyzed. Right/left PI values in manganese exposed group were statistically higher than in control group ($p<0.001$).A positive correlation was detected between serum Mn levels and PI values and MRI T1 hyperintensity. There was no correlation between PI values and MoCA total/subgroup scores or qEEG measures. MoCA total score, abstraction and memory scores were found to be low in workers with T1 hyperintensity. No association between PI values, MoCA total or subtotal scores and qEEG data was determined in Mn exposed workers. When T1 hyperintensity was detected by the clinician on MRI, abstraction and memory were found to be the first cognitive functions affected at that time. These parameters could be used by occupational physicians as a screening test to assess cognition in periodic examinations of welders.

Keywords: Pallidal index, quantitative EEG, welder, manganese

Özet

Mesleki Manganez (Mn) maruziyeti ekstrapiramidal sistem bulgularına ve bilişsel etkilenmeye neden olur. Mesleki Mn maruziyetinin kognisyon ve kantitatif EEG (qEEG) verileri üzerindeki etkisini değerlendirmeyi amaçladık. Bu çalışmaya mesleki Mn maruziyeti olan 175 erkek işçi dahil edildi. Beyin manyetik rezonans görüntüleme (MRI) T1 sekansında pallidal indeks (PI) değeri hesaplandı. Beyin MRI'da T1 hiperintensitesinin varlığı çift kör iki nörolog tarafından değerlendirildi. Kan, spot idrar ve 24 saatlik idrar manganez seviyeleri kaydedildi. MoCA testi toplam puanları ile yürütücü işlevler, dikkat, bellek gibi alt grupların puanları belirlendi. Kantitatif EEG (qEEG) verileri analiz edildi. Manganez maruziyeti olanların sağ ve sol PI değeri, kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek saptandı ($p<0.001$). Serum Mn düzeyi ile PI değeri ve MRI' da T1 hiperintensitesi arasında pozitif korelasyon tespit edildi. PI değerleri ile MOCA toplam puanı, subgrup puanları veya kantitatif EEG verileri arasında herhangi bir korelasyon saptanmadı ($p>0.05$). T1 hiperintensitesi saptananlarda MoCA toplam puanı, soyut düşünme ve tekrarlama puanının düşük olduğu saptandı. Mn maruziyeti olanlarda MRG' de T1 hiperintesitesinin klinisyen tarafından farkedilmesi ile bilişsel fonksiyonların etkilendiği ve bu etkilenmenin öncelikle tekrarlama ve soyut düşünmede olduğu saptanmıştır. Bu parametreler, iş yeri hekimlerince, kaynakçıların periyodik muayenelerinde kognisyonun değerlendirilmesi için tarama testi olarak kullanılabilir.

Anahtar Kelimeler: Pallidal indeks, kantitatif EEG, kaynakçı, manganez,

Received 04.11.2021 Accepted 20.12.2021 Online published 20.12.2021

Akturk T, Celiker G, Sahan MH, Akdeniz G, Tutkun E, Algin O. The Assessment of Effect of Occupational Manganese Exposure on Cognition and Quantitative EEG Variables, Osmangazi Journal of Medicine, 2022;44(4):460-469 Doi: 10.20515/otd.1019283

1. Introduction

Manganese (Mn) is a crucial micronutrient which is existed in the brain at the highest concentration in the human body and required for proper functioning of many organs and systems (1, 2). It is essential for brain growth, development and is a cofactor for some enzymatic reactions involved in neurotransmitter metabolism in central nervous system (3,4). Neurotoxic effects have been identified at high concentrations and frequently emerge from over occupational exposure. Neurotoxicity caused by Mn accumulation in basal ganglia (predominantly globus pallidus) leads to a syndrome called manganism characterized by progressive signs of parkinsonism such as dystonia, bradykinesia, rigidity, a lack of resting tremor and cock gait (5). Mn induced alterations include motor impairment as well as cognitive dysfunction. Dose-related cognitive deficits have been reported in welders exposed to occupational Mn-containing fumes (6, 7).

The quantitative EEG (qEEG) provides information on connectivity and topography of neuronal network by analysing the EEG signals (8, 9). The qEEG measures are associated with general cognition and neuropsychological test scores (10, 11).Slowing of fast-frequency bands (alpha and beta) and increase in slow-frequency bands (delta and theta) activity assessed by qEEG have been reported in Alzheimer's dementia (12, 13). In an other study, it has been showed that qEEG was correlated with cognitive performance in healthy elderly individuals, in patients with mild cognitive impairment and Alzheimer's dementia (14).In addition to Alzheimer's disease, other diseases with cognitive impairment such as Parkinson's disease dementia and Lewy body dementia have also been shown to slow down the frequency of EEG signals (15).

Pallidal index (PI) is a commonly used semiquantitative method, calculated by using T1 weighted sequence of Brain magnetic resonance imaging sections (T1W), showing the level of Mn accumulation in the brain (16).The aim of this study was to evaluate the effect of occupational manganese exposure (serum Mn, urine Mn, PI, T1 hyperintensity) on cognition using MoCA test and analysing qEEG data.

2. Materials and Methods

Study Population

In this retrospective study, a total of 175 male consecutive workers exposed to manganese; of whom 138 were welder and 37 werein metal and battery industry, admitted to Ankara Occupational and Environmental Diseases Hospital between 2014 and 2017 were included. The worker's age, education years, time spent in profession andoccupational group were obtained from each participants medical records. All participants were asked whether they had neurological symptoms and routinely underwent neurological examination.

The workers admitted to our hospital for examination of high manganese levels in the blood or suspicious findings in routine chest radiographs during periodic examination by occupational physicians. The workers were actively working and serum and urine samples of these patients who were referred to our hospital were taken 24-72 hours after a shift.

Patients with liver disease or abnormal liver function tests, drug use for any reason, known neurological disease, alcohol or substance abuse, thyroid disease, systemic disease, vitamin B12 deficiency and folate deficiency were excluded from the study.

The study was conducted according to the guidelines from the Declaration of Helsinki with approval from Ankara Yıldırım Beyazıt University School of Medicine Ethics Committee(Protokol number:23.11.2016/254).

Quantitative EEG

The recorded EEG signals revealed artifacts. In order to remove the artifacts Brain Electrical Source Analysis (BESA v5.1MEGIS Software GmbH, Munich, Germany) was used for data preprocessing. First, for removing the muscular artifacts of high frequency and DC components, a band pass filter was applied (roll off 12 dB octave,

0.3–30Hz). Band pass filter high low 0.16 - 70–notch50. For quantitative analysis, artifact free 45 epochs (30 eye-open, 15 eye-close) lasting 2 s each were gathered. The frequency spectrum was divided into delta band (1.5–3.5 Hz), theta band (3.5–7.5 Hz), alpha band (7.5–12.5 Hz), and beta band (12.5–25.0 Hz). In monopolar montages (A1 A2 as reference), absolute power values were analyzed in the above mentioned bands in all 32 channels. The total power values were calculated by summing the power values of delta, theta, alpha, and beta bands. The number of variables was reduced by calculating regional means of the original variables: frontal region (Fp1, Fp2, Fz, F3, F4, F7 and F8), temporal region (T3,T4, T7, and T8), centroparietal region(Pz, P3, P4, P7, P8, C3 and C4), and occipital region (Oz, O1 and O2).

MRI Evaluation

Brain MR imaging was performed by using 1,5 Tesla system (Initial Ingenia model no: 7813–72; Philips Medical Systems, Netherlands, Tilburg). We calculated the T1W- PI, which is defined as the ratio of the signal intensity (area 0,3 cm2) of the globus pallidus to that of the subcortical frontal white matter on axial T1W images, respectively, multiplied by 100 (17). All measurements were performed by a single radiologist, who calculated PI values did not know the clinical and laboratory data of the workers. Since PI does not have any standard cut-off value, for PI comparison we recruited 50 age-matched and healthy male office workers.

All MRI scans were evaluated by two independent neurologists blinded to clinical or laboratory data. The observers were evaluated globus pallidus on T1W axial section. T1 hyperintensity was classified as present only if both observers agreed.

Manganese Analysis

Blood samples were collected following routine health examination and centrifuged at 3000 rpm for 5 minutes. For manganese analysis, 1 ml serum samples were put into Teflon tubes of microwave oven (MARSXpress, CEM Corporation, NC, USA) and 5 ml nitric acid (HNO3 65%, Merck, Darmstadt, Germany) and ultrapure water were added to the Teflon tubes. After the digestion in the microwave oven, samples were transferred into 50 ml polypropylene tubes and the total volumes were completed to 20 ml with deiodinized water. Samples were stored at +4 ºC until the analysis with ICP-MS (Agilent 7700, Tokio, Japan). The r2 value of the calibration curve of manganese was calculated as 0.9998 with standards (High Purity Standards, Charleston, SC, US). Validation of the method was performed with Certified Reference Materials (Seronorm, Billingstad, Norway).Mn levels in serum, spot urine and 24 hour urine were expressed as µg/L.

Cognitive Assessment

Montreal Cognitive Assessment (MoCA) is a neuropsychological battery that was used to evaluate the function of episodic memory for verbal and visual information, attention, semantic memory, executive function, psychomotor speed and visuospatial skills. MoCA is a short, international screening tool, consisting of one page, with an application time of approximately 10 minutes. Total MoCA scores range from 0 to 30.The validity and reliability of the Turkish version of test was previously approved (18). As a result of the standardization study conducted in our country, especially in the mild stages of the cognitive impairment spectrum, the cut-off score of healthy individuals from those with MCI was 21 (18). Single-blind methods were used by an experienced neurologist. Moreover, participants displayed no audiovisual or motor coordination deficits affecting the test. To account for educational differences, an extra point is added for workers with ≤ 12 years of education (19). MoCA total score, subgroup scores such as executive functions, attention, memory were determined.

Statistical Analysis

Statistical analysis was performed using the software SPSS Statistics 17 (IBM Corporation, Armonk, NY, USA).A Kolmogorov-Smirnov test was carried out in order to determine whether the distributions of continuous variables were normal and the homogenity of variance was analyzed with the Levene test. Descriptive statistics;

mean,standard deviation (SD) and median were used to describe continuous variables and categorical variables are expressed as number of cases and percentages.The significance of differences between groups was analyzed by Student's t-test.The Mann–Whitney U test was used for comparison between groups of non-normally distributed variables, as appropriate. Associations between continuous numerical variables were assessed using Spearman's correlation test.Values of $p<0.05$ were considered statistically significant.

3. Results

Demographics and clinical/labaratory characteristics and MoCA total and subgroup scores of workers exposed to manganese are summarized in table 1. Among workers exposed to manganese 28% were asymptomatic, whereas 72% had neurological symptoms. Headache (45.7 %), forgetfulness (36.6 %) and dizziness (8 %) were most common symptoms. Patients also described irritability, insomnia, aggressiveness, lack of focus and attention, tremor, fatique and confusion.

Table 1. Demographics and clinical/labaratory characteristics and MoCA scores of workers exposed to manganese

	n=175
Age (years) *	39.3±8.6 (18-66)
Education (years)**	8.59 (5-15)
Symptom	
Yes	126 (72.0 %)
No	49 (28 %)
Occupation time (years)**	14 (7-20)
Occupation	
Welder	138 (78.9%)
Metal industry	16 (9.1%)
Battery industry	13 (7.4%)
Others	8 (4.6%)
T1 hyperintensity	
No	144 (82.3%)
Yes	31 (17.7 %)
Serum manganese ** (µg/L)	12.0 (9.6-17.7)
Spot urine manganese ** (µg/L)	0.4 (0.1-1.2)
24 hour urine manganese ** (µg/L)	0.5 (0.1-1.7)
Liver functions (U/L)**	18 (15-22)
AST	20 (15-26.75)
ALT	
MoCA total score **	24 (21-26)
Visuospatial/ Executive	4 (3-5)
Naming	3 (2-3)
Memory	5 (5-5)
Attention	5 (4-6)
Language	2 (1-2)
Abstraction	2 (1-2)
Delayed recall	3 (2-3)
Orientation	6 (6-6)

*AST: Aspartate aminotransferase, ALT: Alanine transaminase. Data are expressed as *: mean ± standart deviation or **:median (25th, 75th percentile). MoCA: Montreal Cognitive assessment.*

The distribution of the urine and serum Mn concentrations are shown in figure 1.

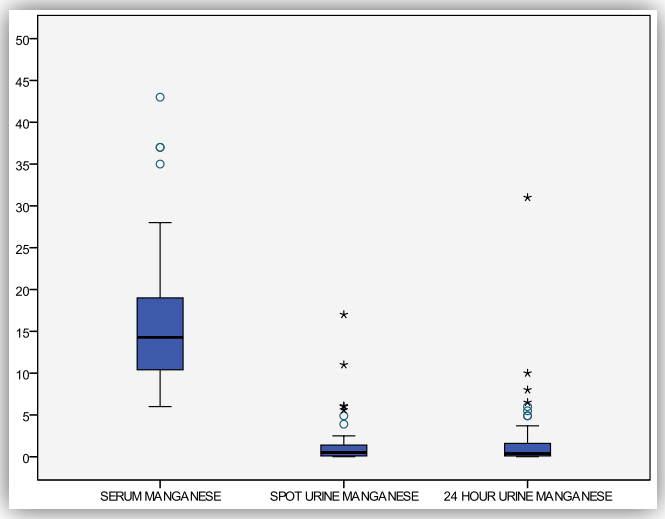

Figure 1. *Serum, spot urine and 24 hour urine manganese level of manganese exposed workers. Mn levels in serum, spot urine and 24 hour urine were expressed as µg/L.*

T1W hyperintensity was present in 31 (17.7 %) cases, all of whom were welder. Magnetic resonance images of the workers exposed to manganese with and without T1W hyperintensity are illustrated in figure 2 and 3.

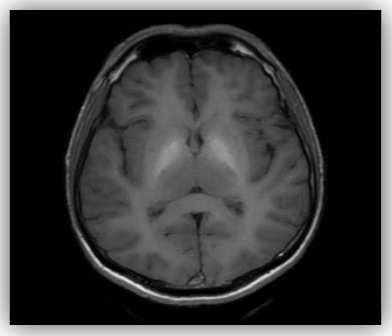

Figure 2. *MRI image of the worker exposed to Mn with TW1 hyperintensity.*

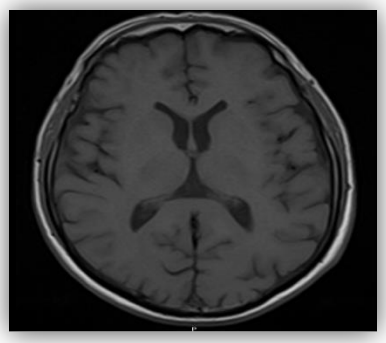

Figure 3. *MRI image of the worker exposed to Mn without TW1 hyperintensity.*

The quantitative EEG data obtainedfrom frontal, temporal, centroparietal and occipital region of workers are shown in table 2.

Table 2. The quantitative EEG data of workers exposed to manganese

	n=175
Frontal	
Delta	12.07 (8.53-24.84)
Theta	7.55 (6.20-17.96)
Alpha	10.03 (7.25-19.64)
Beta	12.41 (8.93-18.87)
Temporal	
Delta	11.42 (8.74-23.15)
Theta	10.27 (8.05-21.69)
Alpha	17.88 (12.30-37.27)
Beta	16.03 (10.23-23.58)
Centroparietal	
Delta	7.68 (4.45-12.90)
Theta	7.22 (4.07-12.75)
Alpha	11.82 (5.88-26.14)
Beta	9.21 (6.81-16.19)
Occipital	
Delta	7.57 (5.85-16.40)
Theta	7.15 (5.06-15.80)
Alpha	15.72 (9.71-36)
Beta	11.9 (8.2-18.23)
Total	
Delta	7.34 (4.45-12.96)
Theta	7.52 (4.10-12.66)
Alpha	12.45 (5.98-26.27)
Beta	9.32 (6.83-15.96)

Data are expressed as median (25th, 75th percentile).

The mean right and left PI values of manganese exposed workers were 107.1 and 106.0 and of control group were 104.2 and 104.1 respectively. These differences observed between the groups were statistically significant (p<0,001). See table 3 for more details.

Table 3. Comparison of PI values between manganese exposed group and control group

	Control group	Exposed group	p-value
Age (years)	38.1±13.3	39.3±8.6	0.502†
T1W PI, right	104.2 (102.2-106.4)	107.1 (104.4-111.7)	**<0.001‡**
T1W PI, left	104.1 (102.3-106.5)	106.0 (103.9-111.1)	**<0.001‡**

† Data presented as mean ± standard deviation (SD), Student's t test, ‡ Data presented as median (25th; 75th percentile), Mann Whitney U test. T1W: T1 weighted sequence, PI: Pallidal index.

Table 4 reports PI values, T1 hyperintensity and correlations with demographic characteristics, manganese values, MoCA test total and subgroup scores. In workers with manganese exposure, increased T1W PI levels were associated with higher serum levels of manganese (p=0.003, r=0.223). But no statistically significant correlation was found between age, occupation time, spot urine manganese, 24-hour urine manganese, MoCA total and subcomponent scores. There was a significant association between T1 hyperintensity and high serum manganese level (p = 0.008) and high spot urine manganese level (p = 0.044). When the MoCA scores were examined, significant negative correlations were observed between

T1 hyperintensity with abstraction (p=0.028), memory (p=0.032) and total score (p=0.040).

There was no statistically significant correlation between qEEG and MoCA total and subgroup scores, left/right PI values and T1W hyperintensity in Mn exposed workers (Table 5).

Table 4. Correlations between PI value, T1 hyperintensity, demographic characteristics, manganese values and MoCA scores in manganese exposed subjects.

	T1W PI, right		T1W PI, left		T1 hyperintensity	
	rho	p	rho	p	rho	p
Age	-0.082	0.280	-0.080	0.294	-0.080	0.296
Occupation time (years	0.102	0.178	0.098	0.196	0.084	0.268
Manganese						
Blood (µg/L)	0.223	**0.003**	0.178	**0.019**	0.200	**0.008**
Spot urine (µg/L)	0.039	0.645	-0.044	0.604	0.169	**0.044**
24 hour urine (µg/L)	0.021	0.831	0.018	0.860	0.053	0.596
MoCA	-0.105	0.172	-0.141	0.065	-0.158	**0.040**
Total score						
Visuospatial/Executive	0.001	0.987	-0.024	0.759	-0.097	0.205
Naming	-0.137	0.073	-0.147	0.056	-0.096	0.213
Attention	-0.109	0.157	-0.145	0.058	-0.138	0.072
Language	-0.123	0.108	-0.135	0.078	-0.123	0.110
Abstraction	-0.118	0.124	-0.144	0.059	-0.168	**0.028**
Delayed Recall	-0.043	0.577	-0.068	0.374	-0.067	0.382
Orientation	0.085	0.270	0.064	0.404	0.090	0.243
Memory	-0.049	0.526	-0.081	0.290	-0.164	**0.032**

T1W: T1 weighted sequence, PI: Pallidal index, MoCA: Montreal Cognitive assessment.

Table 5. Correlations between qEEG data, and MoCA total scores, T1W PI left / right and T1 hyperintensity in manganese exposed subjects.

	MoCA total score		T1W PI, right		T1W PI, left		T1 hyperintensity	
qEEG								
	rho	p	rho	p	rho	p	rho	p
Frontal								
Delta	-0.006	0.936	0.082	0.293	0.085	0.274	0.019	0.805
Theta	-0.039	0.619	-0.051	0.511	-0.035	0.655	-0.029	0.707
Alpha	-0.085	0.278	0.070	0.367	0.064	0.410	-0.058	0.455
Beta	-0.042	0.595	-0.033	0.671	-0.017	0.830	0.018	0.817
Temporal								
Delta	-0.039	0.622	0.063	0.417	0.064	0.407	0.027	0.729
Theta	-0.053	0.499	0.007	0.924	0.013	0.864	-0.015	0.846
Alpha	-0.072	0.357	0.102	0.188	0.088	0.256	-0.067	0.388
Beta	-0.011	0.894	-0.016	0.835	-0.037	0.634	-0.025	0.752
Centroparietal								
Delta	-0.020	0.804	0.075	0.334	0.081	0.295	0.003	0.969
Theta	-0.016	0.842	0.061	0.429	0.042	0.590	-0.026	0.735
Alpha	-0.030	0.705	0.115	0.137	0.100	0.198	-0.517	0.517
Beta	-0.022	0.783	0.012	0.873	-0.005	0.946	-0.064	0.407
Occipital								
Delta	-0.084	0.282	-0.010	0.899	0.010	0.898	-0.041	0.602
Theta	-0.070	0.371	0.015	0.849	0.035	0.654	-0.002	0.984
Alpha	-0.076	0.332	0.092	0.233	0.091	0.241	-0.051	0.512
Beta	-0.053	0.497	-0.062	0.427	-0.059	0.446	-0.051	0.512
Total								
Delta	-0.006	0.943	0.091	0.238	0.095	0.217	0.018	0.814
Theta	-0.012	0.882	0.071	0.356	0.051	0.507	-0.012	0.882
Alpha	-0.040	0.612	0.132	0.088	0.116	0.132	-0.049	0.524
Beta	-0.018	0.818	0.041	0.594	0.026	0.737	-0.030	0.703

qEEG: Quantitative Electroencephalogram, MoCA: Montreal Cognitive assessment, T1W: T1 weighted sequence, PI: Pallidal index.

4. Discussion

Our results suggested that there was no relationship between between PI values and MOCA test total score, subgroup scores and quantitative EEG data in workers exposed to Mn. However, it was determined that MRI T1 hyperintensity observed by clinician was associated with cognitive impairment, particularly affecting abstraction and memory.

A recent review emphasized that Mn exposure had a negative effect on cognition. Regardless of the stage of an individual's lifespan, high and low levels of Mn exposure was shown to negatively affect cognitive function (20). Both low and high Mn concentrations in blood and hair were negatively associated with intellectual development and child IQ scores (21, 22). Mn exposure was adversely associated with cognitive abilities, such as thinking, calculating, reading and learning quotient scores in school-age children. (23). There is increasing evidence that Mn exposure in adults affect cognitive functions negativelysuch as cognitive flexibility deficits, deterioration of visuomotor functions and loss of memory (24, 25). In a functional MRI study it has been shown that brain working memory process was altered by manganese exposure (26). In a study evaluating cognitive impairment in Mn-exposed workers by MoCA test, test scores were found to be lower than the control group (27). Another study evaluating neurobehavioral performance in welders showed a negative correlation between pallidal index value with digit symbol, digit span backward, and showed a positive correlation with stroop test (28). In our study, we did not find any correlation between PI and MoCA total score and subgroup scores, but we found that total MoCA score, abstraction score and memory score were lower in patients with T1 hyperintensity. One possible explanation may be that changes in PI levels are seen earlier, and that Mn accumulation at this level does not yet affect MoCA test results.

The qEEG provides information about some neurological diseases with cognitive impairment. It has been suggested as a biomarker to be used as an aid to early diagnosis of dementia. (29). A recent study demonstrated that qEEG could be a valuable tool for identifying cognitive fluctuations in Lewy Body Dementia (slowing of EEG in LBD compared to AD patients and healthy controls), and for differential diagnosis between dementia types (15). Babiloni et al. stated that progressive atrophy of hippocampus correlates with decreased cortical alpha power in MCI and AD (30). In Parkinson's Disease; slowing in qEEG measures has been correlated with cognitive impairment and could predict future cognitive deterioration; and also, qEEG could provide information about nonmotor symptoms severity and progression (31). Another study has suggested qEEG measures as a marker for cognitive alterations in patients with epilepsy (32). In our study we did not find any significant relation between qEEG measuresand MoCA scores in manganese exposed workers.Protective measures of worker health may have reduced the effect of manganese exposure and thus manganese might not to be at a level to affect cognition. Another possibility is that MoCA scores of the patients included in the study were slightly affected, a study in patients with lower MoCA scores may reveal different outcomesKeski-Säntti et al. did not recommend the use of qEEG in the clinical diagnostics of solvent encephalopathy because of the small amount and unspecificity of the observed abnormalities(33). Chronic occupational toxic exposure may not lead to significant findings in qEEG measures even if they cause cognitive deficits.

Main limitations of this study were that it was a retrospective study and MoCA test was not applied to control group. Other limitations were that air Mn level was unknown (due to lack of preventive and protective measures), all of the subjects were men and only one cognitive test (MoCA) has been applied. A stronger relationship between mn exposure and cognitive impairment has been reported in women (34, 35).Therefore, studies evaluating both sexes or multiple battery of neuropsychological testingwill provide further information.Future prospective studies are needed to determine long-term effects of Mn

exposure on cognitive functions, which will be highly useful for health policies related to occupational manganese exposure.

To the best of our knowledge, the relationship between PI value, MoCA test score and qEEG was evaluated for the first time in workers exposed to manganese. Our results suggested that there was no relationship between PI and MoCA or qEEG in these subjects. In addition, those manganese exposed workers with T1 hyperintensity have increased likelihood of cognitive impairment, particularly in abstraction and memory.These parameters could be used for screening purposes by occupational physicians to assess cognition in periodic examinations of welders.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee of Ankara Yıldırım Beyazıt University School of Medicine (Protokol number:23.11.2016/254)and with the 1964 Helsinki declaration.

Informed ConsentThe research was designed retrospectively.

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