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Welder's lung and brain MRI findings in manganese-exposed welders

Nur Şafak Alici[1*], Türkan Nadir Öziş[2], Gülay Çeliker[3], Tülin Birlik Aktürk[3]

[1]Dr. Suat Seren Training and Research Hospital for Pulmonary Diseases and Thoracic Surgery, Department of Occupational Diseases, Izmir, Turkey
[2]Ankara Occupational Diseases Hospital, Department of Pulmonary Medicine, Ankara, Turkey
[3]Ankara Occupational Diseases Hospital, Department of Neurology, Ankara, Turkey

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Abstract

Background: *Biomarkers of manganese (Mn) exposure and manganism are poorly understood. Blood Mn levels are often used to assess exposure, while brain Mn accumulation may be demonstrated by pallidal hyperintensity at magnetic resonance imaging (MRI). Mn-containing electrodes used in manual metal arc welding may be associated with the welder's lungs.* **Methods:** *A cross-sectional study was set up to compare T1 intensity in basal ganglia at MRI and Mn blood levels in subjects with or without pneumoconiosis. Clinical, radiological, pulmonary function and laboratory parameters were assessed among 154 welders referred to our hospital for suspected pulmonary pathology.* **Results:** *The study group included 123 male welders with pneumoconiosis (79.9%) and 31 welders without pulmonary damage (20.1%). The cases without pneumoconiosis were younger (38.5±6.6 vs 42.1±7.1, p=0.012). Cases with pneumoconiosis had blood lower Mn levels [13.5 (10-21)] as compared to those without pneumoconiosis [18.5 (7.8-34)], p=0.035. In the same groups, the cases with high blood Mn levels were 49 (39.8%) and 18 (58.1%) p=0.052, respectively. Brain MRI hyperintensity was found in 86 (55.8%) subjects with welder's lung 63 (51.2%) but also in 23 (74.2%) individuals without welder's lung. MRI hyperintensity in basal ganglia was significantly related to high blood Mn (p<0.005).* **Conclusion:** *This is the first study evaluating blood Mn levels of welders and their correlation with pulmonary and neurological effects. In Mn-exposed welders, poor working conditions may be associated with exposure fibrogenic fumes leading to chronic lung diseases and hyperintensity in brain MRI suggesting Mn accumulation.*

1. Introduction

Welding is a process of joining metal parts by heating or pressure, and welders work in many branches of industry [1]. According to the US Bureau of Labor Statistics, the number of welders worldwide is estimated to exceed one million. In the USA in 1988, there were 500,000 welders. In 2019 there were still 438,900 welders [2]. In our country, welding is done in 6,417 workplaces, but the number of welders is unknown [3].

Manual metal arc is the most common welding technique, resulting in significant respiratory exposure to complex mixtures of toxic fumes, vapors, and gases containing many hazardous chemical agents (ozone, carbon monoxide, nitrogen oxides and metallic elements) [4]. At high temperatures, metallic particles are oxidized. Generally, oxides of metals in

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*Corresponding Author: Nur Şafak ALICI, MD Dr. Suat Seren Training and Research Hospital for Pulmonary Diseases and Thoracic Surgery, Department of Occupational Diseases, Izmir, Turkey Yenişehir, Gaziler Road No: 331/28, 35170 Konak Izmir Turkey; Email: safak.alici@hotmail.com; Tel: +90(232)433 33 33 / 2112; ORCID: 0000-0001-8546-4418

the form of condensed particles such as iron, chromium, nickel, Mn, and aluminum occur [5]. Typically, the welder should only watch the process at a distance of 50 centimeters and can inhale welding fumes [6]. Exposure varies according to the type of welding and metallic composition of bars, ventilation of the working environment, and characteristics of the protective equipment [4].

Potential adverse health effects include siderosis, pneumoconiosis, metal fume pneumonia, interstitial fibrosis, bronchitis, and Mn poisoning, e.g., neurological, and respiratory changes associated with manganism [7-9]. The welder's lung is a disease that affects the respiratory tract at all levels and parenchyma together following inhalation of welding fumes [10, 11].

Exposure to welding fumes mainly occurs using steel (Mild Steel - MS and Stainless Steel - SS) or carbon steel materials and usually contain Fe (80-95%) and Mn (1-15%) [12]. After inhalation, the absorbed Mn is transported in the blood and crosses the blood-brain barrier (BBB) via specific carriers, selectively accumulating in comparison with other tissues. Mn exposure has been shown to induce a neurological syndrome that resembles Parkinson's disease [13]. The selectivity of Mn accumulation in the basal ganglia has yet to be fully delineated. Several studies showed that an Mn transporter (divalent metal transporter 1-DMT1) is highly expressed in the basal ganglia. Mn promotes neurotoxicity fueling ROS production and causing oxidative stress, thereby impairing mitochondrial enzyme activity and energy production [14]. Elevated blood Mn level is associated with T1 hyperintensity in the basal ganglia at MRI as a biological marker of Mn accumulation. However, T1 hyperintensity in basal ganglia can occur with blood Mn levels within the reference range. Thus, T1 hyperintensity in welders has been recognized as a sign of chronic Mn exposure, a marker of brain Mn accumulation [15-17].

Pathologies that may develop in the lung after inhalation of heavy metals and other toxic or fibrogenic materials in welding fumes are well known. This study aims to assess and compare the blood Mn levels and the resulting central nervous system (CNS) involvement in cases with or without welder's lung. We hypothesized that welding-related Mn exposure would be related to pulmonary and neurological damage and relation with blood Mn levels, and T1 hyperintensity in basal ganglia would be a marker of this damage.

2. Methods

2.1. Study design

This study is a retrospective cross-sectional study conducted in Ankara Occupational and Environmental Diseases Hospital. We accepted consecutive welders exposed to Mn who have admitted to our hospital between January 2015 and August 2019. We used the data of the digital archive system. We retrospectively analyzed clinical, radiological, lung functional characteristics, and laboratory parameters of welders referred to our hospital by occupational physicians suspecting a pulmonary disease. The study group consisted of 154 male welders with welders' lung disease (n=123; 79.9%) and welders without pulmonary parenchymal damage (n=31; 20.1%) employed in steel fabrication factories around our city. Welders used at least one of the following processes: manual arc welding with a covered electrode (MMA), semi-automatic gas-shielded bare wire metal arc welding (MIG-MAG), and manual arc welding with a non-consumable tungsten electrode under inert as shielding (TIG). All subjects were evaluated by a pneumologist, an occupational health physician, and a neurologist. According to the workplace occupational health and safety management reports, all workers had a history of exposure to one or more occupational risk factors in this production process. The managements did not provide ambient measurements because of administrative restrictions in the workplaces.

2.2. Neurological evaluation

Two independent neurologists, blinded to other clinical or laboratory data, performed a neurological examination and a T1 hyperintensity assessment. Globus pallidus was examined in a T1-weighted axial section. Patients considered positive by

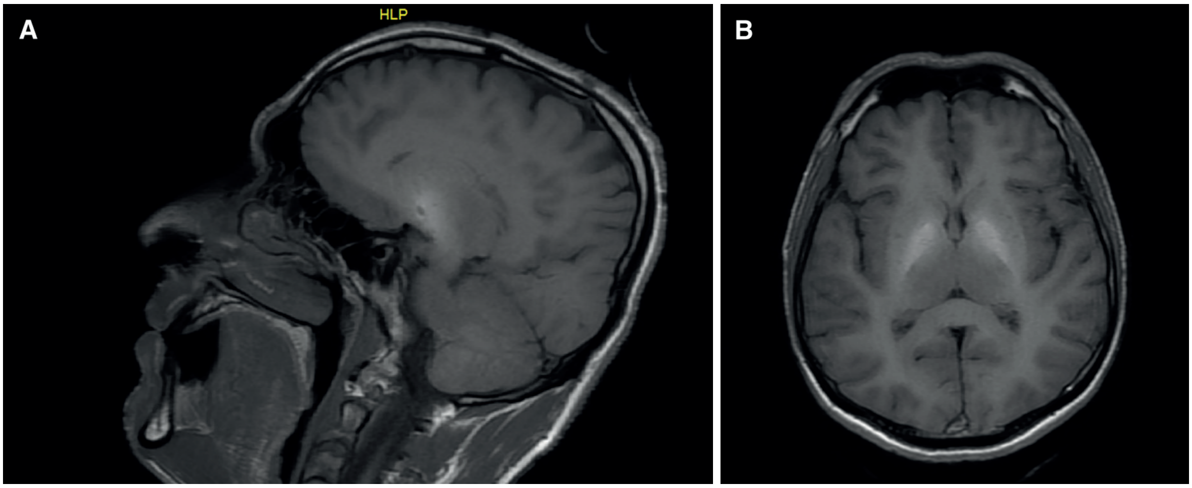

Figure 1. (A and B). MRI sagittal (A) and axial (B) image of a Mn-exposed welder with TW1 hyperintensity.

both neurologists were classified as T1 hyperintensity positive (Figure 1A and 1B). Brain MRI was performed using a 1.5 Tesla system (Ingenia model no: 7813-72; Philips Medical Systems, The Netherlands, Tilburg).

2.3. Pulmonary function assessment

Tests were performed following the American Thoracic Society (ATS) criteria [18]. A standard spirometry measurement was done using dry-seal-spirometry (Zan 100, nSpire Health Inc., Oberthulba, Germany).

2.4. Radiological assessment

Posteroanterior (PA) chest X-rays were taken. A short exposure time with a high voltage technique was used (Trophy UFXRAY, 500 mA, TM). PA chest X-rays were evaluated following International Labour Organization (ILO) 2011 standards [19] and graded by three readers (two chest disease specialists and a radiologist). According to the ILO classification, the ones with profusion 0/1, 1/0, 1/1 and 1/2 have been classified as category 1; the ones with profusion 2/1, 2/2 and 2/3 have been classified as category 2; and the ones with profusion 3/2, 3/3 and 3/+ have been classified as category 3. All subjects whose X-rays with suspect anomalies underwent thoracic high-resolution computed tomography (HRCT). Slices in 1 mm size at 1.5 s intervals which increased by 10 mm with a high-resolution algorithm, were used.

2.5. Blood manganese (Mn) assessment

Blood samples were collected before work shifts and outside the working facilities on Monday (at the beginning of a work week). Inductively-Coupled Plasma-Mass Spectroscopy (ICP-MS) (Agilent 7700X, USA) was used for the analysis of metals in collected samples. Plasma torch argon purity was higher than 99.999%. The method was validated by analysis of certified reference materials (Seronorm Trace Elements, Billingstad, Norway). The detection limit for whole blood Mn levels was 18 ng/ml.

2.6. Statistical analysis

The statistical evaluations have been conducted by computer, using the PASW Statistics for Windows SPSS, Version 21.0 (SPSS Inc, Chicago, IL, USA) package program. Kolmogorov-Smirnov test was used to analyze consistency to normal distribution. Values are presented as median (interquartile range) or mean±SD. The Student's t-test was used for continuous variables, and the Mann-Whitney U test for non-parametric variables to determine the difference between pneumoconiosis and controls.

The chi-Squared test was used to analyze categorical variables. Spearman's test was performed for correlation analysis.

3. Results

A total of 154 welders, 123 (79.9%) cases with Pneumoconiosis and 31 (20.1%) welders without pulmonary parenchymal damage were included in the study. All welders were male; their mean age was 41.4±7.2 (min-max=27-60). Smoking pack years median was 12 (25-75 percentiles=6-20) and duration of exposure was 187.7±74.8 (min-max= 24-384). All of the welders were working without respiratory protection in a non-ventilated space. Clinical data of all workers and workers with or without pneumoconiosis are given in Table 1.

The evaluation of PA chest X-rays according to ILO classification is shown in Table 2. Sixteen (13%) cases were evaluated as category two and above, and large opacity was detected in 2 (1.6%) patients. In HRCT micronodules (n=122, 99.2%), reticular opacities (n=74, 60.2%), lymphadenopathy (n=13, 10.6%), conglomerate masses (n=4, 3.3%), and emphysema (n=21, 17.1%) are detected in patients with pulmonary damage.

The cases without pneumoconiosis were younger (42.1±7.1 vs 38.5±6.6 p=0.012). In patients with pneumoconiosis, the number of smokers was higher than in subjects with normal pulmonary parenchyma: n=112(91.1%) vs n=21(67.7%) p=0.002. Blood Mn levels were higher in cases without pneumoconiosis: 18.5 (7.8-34) as compared to 13.5 (10-21) in patients with welder's lung, p=0.035; likewise, there were more cases with high blood Mn levels: 18 (58.1%) vs 49 (39.8%), p=0.052, in subjects with and without pneumoconiosis, respectively. Brain MRI showed hyperintensity in 86 (55.8%) cases exposed to welding fumes. They all had motor symptoms, like tremors and painful limb spasms, and non-motor symptoms, like dementia and memory loss. Hyperintensity of basal ganglia was observed and higher in individuals without welders' lung: 63 (51.2) vs 23 (74.2) p=0.017. The presence of hyperintensity in basal ganglia was related to the high blood Mn level (p<0.005). When all exposed cases were evaluated,

Table 1. Sociodemographic and clinical data of all welders, and with or without pneumoconiosis.

			Pneumoconiosis		
		All cases	**Yes**	**No**	**p**
Number of patients		154	123	31	-
Age (mean±SD, min-max)		41.4±7.2 (27-60)	42.1±7.1 (27-60)	38.5±6.6 (27-51)	0.012*
Smoking status, n (%)	*Non/ ex smoker*	21 (13.6)	11 (8.9)	10 (32.3)	0.002**
	Active smoker	133 (86.4)	112 (91.1)	21 (67.7)	
Pack years, median (25-75 percentiles)		12 (6-20)	12 (6.25-20)	10 (5-17)	ns†
Exposure time (Mo.), mean±SD (min-max)		19±5 (24-384)	192±76 (48-384)	173±68.8 (24-360)	ns*
Blood Mn (µg/l), median (25-75 perc.)		14,8 (10.9-21)	13.5 (10-21)	18.5 (7.8- 34)	0.035†
High blood Mn, n (%)		67 (43.5)	49 (39.8)	18 (58.1)	0.052**
Basal ganglia hyperintensity, n (%)		86 (55.8)	63 (51.2)	23 (74.2)	0.017**
FEV1 (% predicted±SD)		93.7±14,3	91.8±14,1	97.8±14.4	0.037*
FVC (% predicted±SD)		94.3±14.5	93.1±14.3	99.2±14.6	0.037*
FEV1/FVC (%±SD)		81.6±7,1	81.6±7.4	81.4±6.1	ns*
MEF25-75 (% predicted±SD)		79.1±14.9	78.3±14.1	82.1±17.8	ns*

Mn: manganese ns: not significant
High blood Mn level > 18 ng/ml.
**Indepedent sample T- test.*
***Chi squared test.*
†Mann Whitney U Test.

Table 2. PA chest X-ray of cases with Pneumoconiosis (type and frequency of radiological pattern).

Pattern	Shape and frequency	n=123 (100%)
Small opacity	p	100 (81.4)
	q	21 (17)
	r	1 (0.8)
	s	1 (0.8)
	t	-
	u	-
Profusion	1/0	50 (40.7)
	1/1	45 (36.6)
	1/2	12 (9.8)
	2/1	4 (3.3)
	2/2	6 (4.9)
	2/3	2 (1.6)
	3/3	4 (3.3)
Large Opacity		
	A Opacity	2 (1.6)
	B Opacity	-
	C Opacity	-
Pleural abnormalities		4 (3.3)

blood Mn levels were higher in patients with hyperintense basal ganglia than those without (12.3±5.3 and 19.4±6.8 $p<0.05$).

Among welders with pneumoconiosis, high blood Mn levels occurred more frequently in welders with T1 hyperintensity ($p<0.005$), but no correlation was observed between blood Mn levels and radiological profusion ($p=0.902$).

4. Discussion

In our study, we present the effects of welding fumes on different systems when protective measures are not taken in cases and exposed to welding fumes in primitive working conditions with inadequate ventilation or protection. The most important clinically relevant findings of this study were that the pulmonary system is affected by exposure to welding fumes via inhalation, and the central nervous system is affected by the systemic route. In chronic processes, transition elements such as Mn and fibrogenic materials can accumulate in different tissues and cause damage to other systems. While welder's lung was detected in 123 (79.8%) and Mn accumulation in the globus pallidus in 86 (55.8%) cases of 154 welders exposed to welding fumes, high blood Mn levels were observed in only 67 (43.5%) of all welders. Moreover, the number of subjects with high blood Mn levels was higher among patients without pneumoconiosis. Also, the number of patients with T1 hyperintensity was higher in cases without pneumoconiosis. It should be noted that Mn accumulation in the globus pallidus occurred in 23 (26.7 %) patients without pulmonary damage. In contrast, occupational health physicians focus more on the pulmonary effects of welding fumes than the neurological effects of Mn brain accumulation.

The development of welders' lung disease or pneumoconiosis follows combined exposure to metal fumes and fibrogenic substances such as silica, coal or asbestos in the working environment [20]. In animal studies, fibrosis has been shown with very high doses and long-term exposure to welding fumes, and Buerke et al. detected interstitial fibrosis in electron microscopy examination of CT and biopsy materials of welders who had been exposed to high levels of welding fumes for many years [9] [21]. In our study, welder's lung was detected in 123 (79.8%) cases, and no difference was found between the cases with and without pneumoconiosis in terms of exposure time and smoking pack year ($p>0.005$).

Blood is still recommended as a suitable biological medium for the biomonitoring of Mn exposure, whereas other media (nails, stools, urine) are not. It had been suggested that blood Mn might be helpful as a biomarker for identifying new exposures by inhalation [22]. However, blood Mn concentrations are not as reliable as iron in the past or long-term exposures [23]. Since the blood Mn level is an indicator of short-term exposure, this may be why it is not increased in almost half of the cases with both lung and brain involvement.

Symptoms such as sleep disturbance, headache, mood disorder and EEG disturbances can be observed after exposure to Mn [24]. High-dose and chronic exposure to welding fumes, hence Mn, can lead to the clinical condition resulting in neurological damage called manganism, which causes a range of symptoms resembling Idiopathic Parkinson's Disease [25]. Distinguishing manganism and Idiopathic Parkinson's Disease are challenging, especially in the advanced stages. Both occur with the degeneration of cells in the basal ganglia, which is the center of fine and coordinated movements. In manganism, T1 hyperintensity is seen in brain MRI by deposition of Mn in the globus pallidus in the basal ganglia. T1 hyperintensity in globus pallidus before the high blood Mn levels or Mn toxic effects indicates chronic Mn exposure. It is recommended for use as a biological marker [26, 27]. In our study, hyperintensity in basal ganglia was associated with high blood Mn levels in cases with welder's lungs ($p=0.005$). Still, in welders without pulmonary pathology, there was no difference in blood Mn levels between welders with hyperintense basal ganglia and welders without CNS pathology ($p=0.170$).

The lack of exposure assessment and environmental monitoring, the lack of data on the Pallidal Index and the cross-sectional design were limitations of this study. Also, welders can be exposed to many toxic and fibrogenic particulate matters, not only to Mn. The strength of this study is the concurrent assessment of lung and brain effects associated with exposure to welding fumes and the availability of individual biomonitoring data. However, blood Mn levels are less than ideal biomarkers of recent exposure or accumulation.

5. Conclusions

To our knowledge, this is the first study evaluating blood Mn levels of welders with pulmonary and neurological effects of welding fumes. In summary, our results indicate that Mn and fibrogenic materials exposure resulting from welding fume exposure in poor working conditions may be associated with chronic lung diseases, hyperintensity in brain MRI and Parkinson-like diseases due to accumulation of Mn. Our core message is to improve the awareness of this occupational threat in welding process and the importance of close neurological follow-up of patients diagnosed with welders' lung should be emphasized. Also, for future study design, neurological evaluation and biological monitoring will be added to the follow-up study to evaluate chronic effects of metal exposure.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee (ID: 2021/69-70 date: 10/12/2021).

Declaration of Interest: The authors declare no conflict of interest.

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