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CLINICAL AND PATHOGENETIC FEATURES OF CHRONIC OCCUPATIONAL INTOXICATION WITH FLUORINE COMPOUNDS IN MODERN CONDITIONS

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SUMMARY: Multi-year follow-up of 358 workers of aluminum pot rooms, including 165 individuals suffering from fluorosis, has shown significant changes in the clinical picture of the chronic occupational fluorine intoxication, developed under modern conditions of production, at lower concentrations of fluorine compounds in the air of working area. In this connection, the pathology of the musculoskeletal system plays the dominating role in this clinical picture and has the large variability of combinations of the individual sections destructions of the bone tissue. The main criterion to establish the phase of the disease is still the number and severity of the signs of this destruction. The visceral pathology in contemporary production circumstances is registered with less frequency and loses a number of the previously described clinical manifestations, however, is still of some importance to identify the early signs of the disease and to prevent the fluorosis on time.

Occupational fluorosis (ICD-10: T 59.5; M 85.1) is a chronic intoxication which develops under working conditions due to extended intake of excess fluorine and its compounds. Chronic occupational intoxication with fluorine compounds (COIFC) was first reported in 1932 in Denmark when changes in the lungs and unusual massive impairment of the bones were found in cryolite plant workers [13]. Three radiological phases of sequentially developing bone changes were established.

In recent years, the COIFC issue was addressed by thousands of studies in different countries. Fluorine and its compounds cause multiple metabolic disorders in various organs and systems of aluminum industry workers and also have the ability to accumulate in the body. For over 70 years, the staff of FBSI [Federal Budgetary Research Institute] EMRC PHPIW [Ekaterinburg Medical Research Center of Prophylaxis and Healthcare of Industrial Workers] of Rospotrebnadzor [Russian Agency for Healthcare and Human Rights] have been working on issues of etiology, pathogenesis, clinical manifestations, treatment, and prevention of COIFC [3, 4, 6, 7, 10]. In recent decades, the total fluorine exposure load on workers in the electrolysis facilities of Ural aluminum manufacturing plants has decreased [9]. Therefore, it has become highly relevant to study the changes in clinical patterns of fluorine intoxication.

Materials and methods. Over the last decade, 358 workers in electrolysis shops at aluminum manufacturing plants underwent in-depth examinations at the clinic of FBSI EMRC PHPIW of Rospotrebnadzor. We had conducted a study on the clinical development of fluorosis under modern production conditions at lower concentrations of fluorine compounds in workplace air with 165 patients suffering from fluorosis. The age at diagnosis ranged from 36 to 63 years (mean age – 53.8 ± 0.6 years), and length of service under conditions of exposure to fluorine compounds ranged from 12 to 41 years (mean length of service – 24.9 ± 0.7 years). The first stage of the disease was diagnosed in 74 cases, the second – in 91 (mean age – 52.0 ± 0.4 and 53.4 ± 0.7 years; mean length of service – 23.7 ± 0.6 and 25.8 ± 0.8 years, respectively). The dynamics of development of long-term effects was studied for 1 to 10 years in 78 patients suffering from COIFC.

Results. Currently, the most common complaint of fluorosis patients is constant, aching pain in the joints, most often in the knee (93.8%), elbow (91%), or shoulder (61%), and less frequently (46.3%) in other joints. The genesis of pain in fluorosis is complicated; it is due to the direct toxic effects of fluorine on the cartilage and periarticular tissues. Upon progression of the articular process, start-up pain and vascular pain may also develop due to impaired intraosseous circulation, both arterial and venous stasis. Ostealgia of the shins is observed in 41.6% of cases and of the forearms – in 39.3%, regardless of the stage of COIFC. The mechanism of algic syndrome in COIFC patients is driven by both the change in the mineral composition of osseous tissue and by the impairment of intraosseous blood flow, leading to disruption of the intraosseous

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pressure and to re-irritation of the intraosseous receptors [1, 11, 12]. Muscle cramps, mainly in the calf, occurred at rest and at night in 30.3% of patients. The cramps are probably caused by a negative calcium balance in the body.

On examination, no severe deformation of joints or evidence of active inflammation was found. The majority of patients indicated tenderness on palpation and in motion with limited mobility of elbow and knee joints; at the same time, functional activity is independent of the stage of COIFC.

The most common radiographic symptom of osseous tissue restructuring with COIFC, found in 77.0% of patients in stage 1, and in all (100%) patients in stage 2, was an increase in osseous tissue density above 15 on a standard step-wedge (see table). This symptom develops on introduction of fluorine into the hydroxyapatite, constituting one of the fractions of the mineral phase of the bone. Fluorine replaces the hydroxyl ions to form stable fluorapatite which leads to an increase in mineralization and increased osseous tissue density. The second prevalent symptom was the endosteal reaction in the form of narrowing of the medullary canal in 66.2% of patients in stage 1 of COIFC and in 96.7% of those in stage 2 (p <0.001), and an increase in the hyperostosis index over 3.0 in 78.3% and 95.6% of patients, respectively (p <0.01). In third place was a symmetrical periosteal reaction in the form of overlays and irregularities on the medial and posterior outlines of the tibiae identified in 92.3% of patients in stage 1 and 66.2% of those in stage 2 of COIFC (p <0.001).

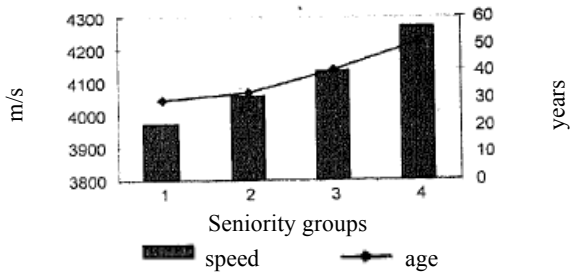

Fig. 1. Speed of the sound wave traveling through bone as a function of length of service and age

To evaluate the osseous tissue density as a function of occupational fluorine exposure load, ultrasound densitometry was performed on 660 workers of principal occupations in electrolytic aluminum production with a length of service from 2 to 33 years and 16 patients with fluorosis. Analysis of the results of the speed of sound (SOS) measurements during passage of the ultrasonic wave was carried out on groups with less than 5, 5-9, 10-19, and over 20 years of service. The length of service and age of the subjects were directly correlated. It is known that increase in age is associated with decrease in density and changes in osseous tissue accompanied by development of osteopenia and osteoporosis [2]. Instead of the expected decrease in SOS in older age groups, a distinct increase in this parameter is observed with an increase in length of service (Fig.1). At the same time, the speed of sound through the bones of COIFC patients significantly exceeded that of workers with extended length of service (4,318.8 ± 59.5 m vs. 4,065.9 ± 33.2 m, p <0.001). The findings suggest that ultrasound densitometry provides objective data on osseous tissue density in numerical terms, allows for monitoring the dynamics of change, and can be used as an informative criterion for the diagnosis of COIFC.

According to the toxicokinetics, up to 80% of the absorbed fluorine is excreted by the kidneys. Its excretion after shift change showed a significant increase for workers with extended length of service. Lower urinary excretion of fluorine after shift change by workers with less seniority reflects the ongoing process of its accumulation in unsaturated sites, mainly in the bones. The fluorine concentration of urine of patients with stage 1 fluorosis was 1.2 ± 0.1 mg/L and those of stage 2 – 1.5 ± 0.2 mg/L, showing a statistically significantly excess over the control level

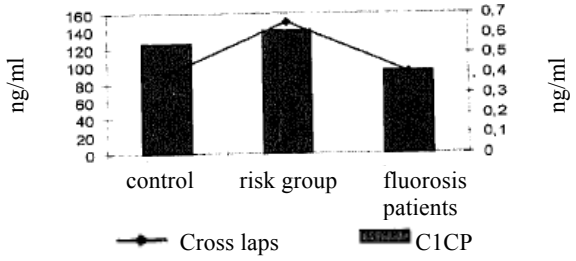

Fig. 2. Levels of osseous markers in examined workers

(0.93 ± 0.08 mg/L; p <0.05). Correlation analysis confirmed the link between the fluorine excretion level in urine and duration of fluorine exposure (r = 0.61 ± 0.13; p <0.05).

Moderate correlation between urinary excretion of fluorine and hydroxyproline confirms the impact of fluorine on bone collagen metabolism. The established correlation between urinary excretion of fluorine and increased activity of MDA (r = 0.64 ± 0.11; p <0.05) confirms the influence of fluorine on free radical oxidation processes.

The following markers, derivatives of type 1 collagen, are objective criteria of bone tissue rearrangement: procollagen type 1C-terminal peptide

(C1CP), reflecting changes in the synthesis of type 1 collagen, and C-terminal telopeptide (β-Cross Laps), being a degradation product of type 1 collagen. In examinations of individuals exposed to fluorine compounds, an increase in the blood content of C1CP was registered in 26.9% of cases, normal level in 31.3%, and a decrease in 41.8% of cases; β-Cross Laps, respectively, in 3.0, 65.7, and 31.3% of cases. Their mean values were 115.6 ± 9.8 and 0.522 ± 0.09 ng/mL. Statistically significant lower values of both S1SR and β-Cross Laps (84.9 ± 10.1 and 0.284 ± 0.06 ng/mL, respectively; $p < 0.05$) were registered for the fluorosis patients. As determined from bone markers of synthesis and destruction of osseous tissue, patients with fewer years of service exhibit increased osteosynthesis processes, and COIFC patients – impairment of its metabolism (Fig. 2).

Examinations have revealed certain functional changes in the gastroduodenal and hepatobiliary systems: elevated activity of transaminases in a third of the patients, levels of β-lipoprotein in 37.5%, and cholesterol in 33.5%. Hyperglycemia was recorded in only 9% and dysproteinemia in 2.3% of patients. On the basis of clinical and laboratory data confirmed by ultrasound studies toxic hepatitis was diagnosed in 15.7% of subjects after exclusion of other factors which could cause liver damage (viral, alcohol-based, nutritional, and other).

Fluorine and its compounds exhibit cardiovasotoxic action. The leading syndromes of cardiovascular system impairment due to fluorosis are manifestations of autonomic vascular dysfunction and myocardiodystrophy. In our studies, 6.2% of patients were diagnosed with coronary heart disease, 52.1% with hypertension (stage 2 hypertension was more frequently associated with stage 2 of intoxication). Myocardiodystrophy was detected in 11.9% of cases and has been deemed to be the result of the toxic effects of fluorine compounds on the heart muscle upon exclusion of all other etiological factors. These changes in the cardiovascular system have been largely non-specific in nature and may be associated with the impact of fluorine on calcium metabolism due to its affinity not only with collagen but also with calcium [8].

The earliest clinical manifestation of almost any occupational disease, including fluorine intoxication, is vegetative dystonia syndrome (VDS). The disorders identified in examined patients (32.7%) fit into one of the forms of VDS –psychovegetative syndrome (mainly astheno-vegetative) with permanent and paroxysmal disorders of sympathetic or parasympathetic orientation.

Impairment of the peripheral nervous system in the form of sensory autonomic poly-neuropathy of the upper and lower extremities, confirmed by electromyography, was reported in 10.7% of patients. Along with impairment of segmental (peripheral) segments, a significant role in the development of these disorders is played by changes to the suprasegmental (central) vegetative structures.

Combined effects of elevated concentrations of fluorine and industrial dust also impacts the health of the airways. Impairments of the upper respiratory tract were detected in 36.7% of patients. At the same time, subatrophic pharyngitis was found in 39.3% of cases, catarrhal rhinopharyngitis in 3.4%, compensated tonsillitis in 1%, and vasomotor rhinitis in 0.5% of cases. No ulcerous-necrotic changes or perforation of the nasal septum were found in workers at modern production facilities. Based on the data of instrumental studies (bronchoscopy and respiratory function tests), 26.5% of COIFC patients were diagnosed with chronic bronchitis. During initial diagnosis of the disease, occupational toxic-dust bronchitis was accompanied in 44.8% of cases by respiratory failure (RF) of the 1st degree, in one-half of the patients (49.2%) – 2nd degree, and in 6.0% of cases no signs of RF were found. Asthma attacks were registered in a number of individual patients (3.4%) as well as dry wheezing upon extended exhalation which, in conjunction with additional examination data (PEFR and bronchodilator tests), were diagnosed as bronchial asthma. Positive allergy tests for industrial allergens (nickel, lithium, chromium, etc.) helped to confirm the occupational genesis of the asthma in 0.6% of cases.

It should be noted that currently no one has been diagnosed with stage 3 [fluorine] intoxication, due on the one hand to improvement in working conditions at the workplace and, on the other, to early detection of symptoms of the disease and implementation of preventive health measures.

Monitoring the health of fluorosis patients showed that further progression of intoxication depends on continued or terminated contact with fluorine compounds. Patients suffering from stage 1 fluorosis, continuing to work under the same conditions, exhibit a build-up in bone restructuring processes in the form of increasing hyperostosis index in 2-4 years and an increase in osseous tissue density after 8-10 years of observation. In patients who have stopped working, the bone restructuring processes were less pronounced and continued only in the early stages – up to 4 years after separation from hazardous production, which points to the need for sustainable employment immediately upon diagnosing stage 1 fluorosis.

C o n c l u s i o n s . *1. At lower concentrations of fluorine compounds in workplace air, the clinical*

pattern of COIFC suggests a dominant role of musculoskeletal pathology in the clinical picture of fluorosis. At the same time, great variability is noted in impairment combinations of individual sections of osseous tissue. The identified changes do not differ qualitatively or quantitatively from those previously described which are associated with exposure to higher concentrations of fluorine and its compounds in workplace air. 2. The number and severity of symptoms of osseous tissue impairment remains as the main criterion for defining the stage of the disease. Visceral pathology, part of the COIFC syndrome complex formerly considered mandatory, is now recorded less frequently and has lost a number of previously described clinical manifestations. 3. The characteristic syndrome of at least three impaired systems (gastroduodenal, hepatobiliary, nervous, or cardiovascular) has practically been eliminated. Only a few individual symptoms of the pathology of these systems occur in individual patients.

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