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Metal fume fever (review). Part 2

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Abstract. The pathogenesis of metal fume fever is based on non-specific, non-allergic activation of macrophages or pulmonary epithelial cells with local and systemic release of pyrogenic chemotactic mediators. This is confirmed by an increase in the number of inflammatory cytokines and acute-phase proteins in the onset of metal fume fever. Interleukin-6 is an early, highly sensitive biomarker of exposure to zinc- and copper-containing metal vapours. Oxide particles or released matrix metalloproteinases act as allergens, or zinc oxide acts as a hapten and combines with protein to form a complete antigen. There are 17 main symptoms of metal fume fever and there is currently no specific test to diagnose it. Treatment options are limited to symptomatic relief, including analgesics, nonsteroidal anti-inflammatory drugs and salicylates, antacids and antihistamines, bronchodilators and, if necessary, cardiovascular drugs, oxygen therapy and alkaline inhalation. In severe syndromes with reduced oxygen saturation, the initial treatment is high-flow nasal oxygen therapy. In most cases, the prognosis is positive, with rapid and complete recovery within 12 to 48 hours of cessation of exposure to metal fumes. Adequate occupational hygiene should be maintained to prevent the occurrence of inhalation fever.

Key words: metal fume fever, pathogenesis, clinic, treatment, prognosis, prevention.

Pathogenesis

The pathogenesis of metal fume fever (MFF) is based on non-specific non-allergic activation of macrophages or pulmonary epithelial cells with local and systemic release of pyrogenic chemotactic mediators. The mechanism of MFF is not fully understood, but it is thought to be associated with systemic neutrophilis and cytokine activation, usually with increased concentrations of IL-6 and IL-8 [1–3].

This is confirmed by an increase in proinflammatory cytokines and acute phase proteins at the onset of metal fume fever. TNF-α, IL-1β and IL-6, which act as endogenous pyrogens, are considered to be the main direct triggers of febrile illness and its associated symptoms. TNF-α and IL-1 stimulate each other's production through positive feedback, and IL-1β and TNF-α are potent inducers of IL-6 production [4]. Thus, under the influence of endopyrogens, the 'set point' of the hypothalamic thermoregulatory centre is adjusted to a higher level and the reference point for normal temperature is shifted upwards. The new temperature regime is now taken as the basis for regulation, and the body does everything necessary to ensure that the already elevated temperature is maintained.

IL-6 is an early, highly sensitive biomarker of exposure to metal vapours containing zinc and copper [5]. The development of systemic inflammation occurs in parallel with an increase in serum IL-6 levels, which can be observed as early as 6–10 hours after exposure to metal vapour, with a dose-dependent acute phase response [4–7]. TNF-α levels peak 3 hours after exposure to metal aerosols and appear to play an important role in the development of MFF. These cytokines may be the pyrogens that cause the febrile state [8].

Several studies have shown an increase in C-reactive protein (CRP) after single and repeated exposure to zinc and copper welding fumes [9–14], that is not specific [8]. For metal aerosol containing 1.20 to 1.50 mg/m^3 of zinc, the highly sensitive CRP increased the day after exposure. No increase in CRP was detected at air pollution levels of 0.90 mg/m^3 [15]. In an experiment on volunteers, an increase in serum CRP levels was found 24 hours after exposure to welding fumes during the brazing of metals using inert gas [6]. Other studies have shown an increase in serum CRP and acute phase amyloid A protein 29 hours after exposure to zinc and copper metal aerosols [4, 5, 7].

Chronic increases in CRP and myeloperoxidase indicate an increased cardiovascular risk, which was determined in volunteers exposed to welding fumes containing zinc and copper [4, 7, 10, 13].

The interaction of immune factors promotes inflammation, leading to the involvement of neutrophils and a systemic response in the form of fever [8]. Laboratory tests may show nonspecific leukocytosis with a left shift [3, 11, 16–19].

Neutrophils, monocytes and acute phase proteins in the blood increased 22 hours after exposure to micro- and nanoscale ZnO [4, 7, 10]. Over time, neutrophilic leukocytosis changes to lymphocytosis [17]. Nonspecific markers of inflammation are elevated, and the erythrocyte sedimentation rate sometimes reaches 120 mm/h [11, 12]. Moderate anaemia, basophilic erythrocyte granularity, transient hyperglycaemia, and increased bilirubin levels are noted [17].

Traces of protein, leucocytes, cylinders, porphyrin, often porphyrin, are found in the urine, the amount of urobilin is increased [17]; urinary α_1-antitrypsin and inter-α-trypsin H4 heavy chain inhibitor may indicate early lung function decline in metal fume exposed shipyard workers, highlighting the need for better health and safety monitoring to reduce respiratory risks [20].

Serum levels of inflammatory markers showed a significant increase compared to baseline 6 or 24 hours after the first exposure and remained elevated throughout all subsequent exposures [13].

In some rare cases, allergic mechanisms may be involved in the pathogenesis of MFF, but then metal fume fever may be either a misnomer or superimposed on bronchial asthma or hypersensitive pneumonitis [3, 4]. Cases of IgE-mediated immunological reactions causing urticaria and angioedema during an acute episode of MFF have been described and confirmed by others [4, 8, 17, 21, 22]. This is because the effector mechanisms can overlap and cause similar symptoms. The mechanism of a type I hypersensitivity reaction involves the activation of Th_2-lymphocytes, which induce B-lymphocytes to produce IgE antibodies. These antibodies bind to high-affinity FcεRI receptors on mast cells and basophil granulocytes. After secondary exposure to an allergen, the cross-linking of IgE antibodies on these cells causes them to be activated and release mediators such as histamine, enzymes, heparin, prostaglandins and leukotrienes, leading to the characteristic symptoms [4].

Various hypotheses have been proposed, such as oxide particles or released matrix metalloproteinases acting as allergens, or zinc oxide acting as a hapten and forming the full antigen in complex with protein. It is possible for the immune system to produce an antibody against the Zn-containing antigen, forming an immune complex with it, and it is also possible to produce secondary antibodies against the primary immune complex. Depending on whether the primary immune complex or the secondary antibody concentration dominates, the body may develop either tolerance or MFF [4]. These conditions have some clinical overlap with hypersensitivity pneumonitis, a lung disease caused by bioaerosols and certain chemicals that induce specific cellular and humoral immune responses [3].

Clinic

There are 17 leading symptoms of MFF, in the vast majority of cases the number of registered symptoms ranged from one to seven:

- Fever — 51%
- Abdominal cramps — 8%.
- Rash — 4%.
- Diarrhoea — 8%.
- Dizziness/vertigo — 8%.
- Muscle weakness — 19%.
- Tachycardia — 50%.
- Hypotension — 8%.
- Chill — 25%.
- Shortness of breath — 8%.
- Ailments — 14%.
- Cough/wheezing — 11%.
- Flu-like symptoms — 100%.
- Headache — 23%.
- Nausea/vomiting — 11%.
- Myalgia — 19%.
- Tongue paresthesia — 1% [22, 23].

MFF debuts as an acute attack, which is similar to malaria or influenza and usually occurs in three stages.

1. *The latency* period lasts from the moment of inhalation of highly dispersed aerosol vapours until the first signs of the pathological process appear. The onset of MFF symptoms is delayed by 3 to 10 hours (rarely up to 48 hours) after exposure to the pathogenic factor; symptoms may appear after the worker has completed the shift, making it difficult to identify a link between symptoms and occupational exposure [1, 6, 8, 11, 18, 22–24]. During this period, respiratory damage develops in the form of denaturation of their protein structures and the release of these substances into the bloodstream. There are no clinical symptoms [17, 24].

2. *The prodromal period* lasts 4–5 hours. There is conjunctival and pharyngeal hyperaemia and scleral injection. Some of the first characteristic symptoms are excessive salivation, sweetish/metallic taste in the mouth associated with throat irritation, shortness of breath and thirst, abnormal taste sensations, general malaise, headache, weakness, nausea, vomiting, drowsiness. dry, non-productive, hacking cough, chest and back pain, difficulty breathing, shortness of breath, chills with excessive sweating, chills and shivering, subfebrile temperature, myalgia, arthralgia and fatigue. Only a quarter of patients experience respiratory symptoms. In the prodromal period, pulmonary ventilation disorders are reflexive (bronchospasm, bronchiolospasm). The results of physical examination of the lungs are usually normal, sometimes high-frequency whistling sounds (wheezing) or rales are heard. The most common objective signs are fever and sinus tachycardia. Abdominal pain, nausea, and vomiting are rare [1, 3, 4, 6, 10, 11, 13, 18, 19, 25].

3. *The immediate feverish phase* («real fever») lasts 5 to 8 hours. Sometimes symptoms peak after 18 hours, and MFF is diagnosed within the last 48 hours of exposure to metal vapour [8, 22]. The condition is characterised by a sharp rise in body temperature to 39–40° C, the patient has redness of the skin, chills, shivering, generalised tremor, headache, drowsiness, delirium, loss of consciousness, pupil dilation. Tendon reflexes are increased. Allergic manifestations in the form of urticaria and rarely angioedema are possible. Myalgia and arthralgia may be observed. Shortness of breath is noted and the development of unilateral or bilateral pneumonia, sometimes without fever, cannot be excluded. X-rays may show a blurred lung pattern or small-focus bilateral diffuse shadows. Gastrointestinal disturbances (abdominal pain, nausea, vomiting, diarrhoea) and a slightly enlarged and tender liver may be present. Initial chest x-ray findings are usually without pathological signs, but mild vascular congestion may be observed, and in severe cases diffuse patchy infiltrates and progression to acute respiratory distress syndrome (ARDS) may be seen. A pulmonary function test in the acute phase may show a decrease in lung capacity, which normalises with recovery. Pulse oximetry is usually normal. Laboratory tests are not required in most cases but may show leukocytosis with a left shift, followed by lymphocytosis, increased erythrocyte clotting rate, transient hyperglycaemia and increased inflammatory markers. Traces of protein, leukocytes, casts, increased amounts of urobilin and porphyrins are detected in the urine. This is followed within a few hours (usually 5–8) by a sharp lytic drop in body temperature, accompanied by profuse sweating. Deep sleep ensues, after which the patient's condition is significantly improved [1, 11, 17, 22–24, 26].

Over 90% of MFF cases are mild [8]. As a rule, this is a benign and self-limited pathological process that disappears within 12 to 48 hours after exposure to metal vapour is stopped and does not require special treatment [1, 8, 11, 18, 22, 23, 27], followed by short-term tolerance to zinc oxide vapour, which disappears within one to two days after avoiding the provoking factor [23]. It often takes four days for full recovery [4, 11, 18, 23], but symptoms may reappear with repeated exposure [1, 14].

Although metal vapour fever is usually benign and mostly resolves on its own, severe cases have been reported, particularly in patients with pre-existing respiratory disease. ARDS with fever, hypoxia, tachypnea, pneumonitis, pericarditis and aseptic meningitis requiring mechanical ventilation are rare [1, 8, 11, 18]. Complications may develop in the form of focal pneumonia or toxic pulmonary edema [17].

The disease can recur if a person is repeatedly exposed to metal vapours [4]. Repeated exposure to these substances and attacks of metal fever cause changes in the body's immunological reactivity, activation of the endogenous microflora, and a decrease in tolerance to external infectious agents [17].

Repeated exposure to metal vapour can cause tachyphylaxis (*greek: ταχύς* — fast; *φύλαξις* — immunity, protection) — a sudden acute decrease in sensitivity to a particular substance after its administration, i.e. the development of tolerance. This may occur after an initial dose or after a series of exposures to low concentrations. Increasing the dose of a substance can sometimes restore the initial inflammatory response [17, 28]. One theory of MFF tolerance is that the synthesis of the protein metallothionein is induced, which binds heavy metals and prevents their accumulation [22], and others suggest that tolerance is provided by competition between two types of antibodies [4]. In some reported cases, symp-

toms of MFF have disappeared during the period of re-exposure. This phenomenon is known as 'induced transient immunity' and can last as long as exposure is repeated every other day. If there is a break in exposure of two days or more, symptoms may reappear. Temporary immunity may explain why MFF often recurs in workers who are not regularly exposed to metal vapour [4].

Continuous exposure to metal aerosols over a week often results in tachyphylaxis, with the most severe symptoms following a period of non-exposure (e.g. weekends) and improvement during the working week. In a retrospective review of cases, the most common day of symptom onset was Monday, with a steady decrease in the incidence of MFF during subsequent working days of the week [24]. Unlike symptoms that do not reappear with repeated exposure, systemic inflammation can persist, indicating a potential risk to welders [10, 29]. As for stereotypical symptoms that have developed over many years, they can occur regularly, associating sudden fever up to 40° C, morning nausea, night sweats and chest pain with pleural characteristics [19, 30]. Symptoms are usually mildest on Sunday and worst on Monday and Tuesday after returning to work. There is improvement during the working week, but re-exposure to the pathogen after returning to work leads to a return of symptoms such as fever, malaise and wheezing. This is why it is sometimes called 'Monday morning fever' [8, 19]. Most of the symptoms occurred on Monday (24–35%) and Tuesday (21%), with the fewest on Sunday (3–4%) [11, 17, 18].

There is currently no specific test available to diagnose MFF [23]. Due to the similarity of symptoms to influenza-like illness, MFF remains an under-diagnosed pathological condition [1, 4, 14, 22, 23]. The verification of the disease is primarily based on clinical data, anamnesis, exposure and time of onset of symptoms of metal vapour exposure [1, 22, 23, 25, 27].

The occupational nature of the disease is usually fairly easy to establish. The nature and conditions of work, sudden onset, clinical features, recurrence and group nature of the disease should be taken into account [27, 31].

There is little information in the literature on the long-term effects or complications of the pathological effects of metal oxide fume. It has been hypothesised, but not conclusively proven, that MFF may lead to long-term cases of occupational asthma. Chronic exposure to extremely high concentrations of zinc oxide vapour or dust for more than six months may contribute to the development of bronchial asthma, chronic obstructive pulmonary disease, pneumoconiosis and other pulmonary fibrosis (chronic beryllium disease, 'cobalt lung'), lung cancer, dermatitis, furunculosis, conjunctivitis and gastrointestinal disorders [11, 18, 23, 32]. In case of acute exposure to cadmium vapour, restrictive lung disease can last for life [33].

Treatment

The condition is usually mild and resolves on its own [8]. Long-term treatment of MFF is quite rare [24]. In more severe cases, hospitalisation may be required for intravenous hydration and cooling [1]. Treatment of fever caused by metal fumes is mainly supportive and symptomatic. The first line of treatment is to give plenty of sugary drinks (and oral rehydration in the case of dehydration), warmth (warm baths) and bed rest [1, 8, 11, 14, 17, 18, 31].

Treatment options are limited to symptomatic relief of the disease, including analgesics, non-steroidal anti-inflammatory drugs (antipyretics) and salicylates, antacids and antihistamines, bronchodilators and, if necessary, cardiovascular drugs (cardiac glycosides), oxygen therapy, alkaline inhalation. Intravenous administration of 40% glucose solution with ascorbic acid (300 mg) is indicated. The development of pneumonia is an indication for the use of antibacterial agents (amoxicillin/clavulanic acid) [4, 17, 26, 31].

It is not recommended to prescribe oral or intravenous corticosteroids a priori, as their effectiveness in metal smoke fever is not supported by a specific evidence base [11, 18, 33]. However, if the bronchospasm is severe (asthmatic status), glucocorticoids (dexamethasone, methylprednisolone) and inhaled non-selective $ß_1$-, $ß_2$-agonists (nebulised salbutamol) may be useful [4, 8, 14, 17, 26, 31].

In severe MFF with a decrease in oxygen saturation in the pre-hospital stage (very rare — up to 80%), the initial treatment is high-flow nasal oxygen therapy (the development of oxygen dependence is not excluded) [8, 26]. In the case of severe hypersensitivity pneumonitis, bilevel positive airway pressure and endotracheal intubation may be considered [8].

There are practically no recommendations in the available literature on the use of chelators and other heavy metal antidotes for the treatment of MFF, as there is no clear evidence base for their efficacy in metal fever, since the primary mechanism of development of this pathological condition is an inflammatory reaction, not metal intoxication [33].

It is therefore very important to distinguish between MFF and life-threatening inhalation poisoning by heavy metals (thallium, mercury, arsenic, beryllium, cobalt, etc.) and their compounds, which often cause fever [31, 33, 34]. If intoxication with heavy metal compounds is suspected, even if the MFF is overlaid with a severe poisoning clinic, in addition to oxygenation and respiratory therapy, repeated gastric lavage with the introduction of enterosorbents and intestinal lavage is performed, complete detoxification, antidotal and symptomatic therapy using radical detoxification methods such as forced diuresis, peritoneal dialysis, haemodialysis, haemosorption, plasma sorption, plasmapheresis and hyperbaric oxygenation [35, 36].

Inhalation of zinc chloride aerosol when using a smoke bomb is associated with a life-threatening combination of MFF and inhalation chlorine poisoning, as evidenced by the presence of a period of moderate recovery. This results in severe ARDS with severe parenchymal respiratory failure. Such patients require prolonged protective mechanical ventilation in the PCMV-APV mode with high PEEP (up to 20 cm H_2O) against a background of artificial myoplegia. Early prone positioning results in effective alveolar engagement during the acute exudative phase of ARDS, improving oxygenation by minimising blood shunting in patients with severe refractory hypoxaemia. Clinicians have successfully used the prostacyclin drug epoprostenol by continuous inhalation at a dose of 0.05 µg/kg/min with a gradual decrease in concentration over 48 hours, although there are currently no powered randomised clinical trials of the efficacy of inhaled prostaglandins in the treatment of ARDS. Intravenous and nebulised N-acetylcysteine increases urinary zinc excretion. L-3,4-dihydropyridine is used to stop collagen deposition in the lungs, and intravenous methylene blue is effective in treating methaemoglobinaemia. High doses of corticosteroids over a long period of time may be useful for the intensive care of severe ARDS caused by smoke bomb aerosol and should be considered as the only method of pharmacological treatment in combination with protective ventilation. The use of ECMO (extracorporeal membrane oxygenation) in severe metal fume-induced ARDS has not been adequately evaluated in prospective studies [3, 12, 37].

Forecast

MFF, when not combined with severe inhalation poisoning with heavy metal compounds, is usually a benign process that resolves in one and a half to two days [8], and the prognosis in most cases is positive with a rapid and complete recovery within 12 to 48 hours after cessation of exposure to metal fumes [17,

24, 31]. Temporary disability usually lasts 5–7 days, but is significantly prolonged in the event of pneumonia or an exacerbation of any chronic disease. Metal fume fever ends with a full recovery, and the process is usually not chronicised [17, 31].

Although MFF episodes are self-limited, they can be the first warning sign for people who do not follow safety precautions at home or at work, and can eventually lead to the development of chronic respiratory disease [22]. Welders, who are mainly exposed to metal fumes containing zinc and copper, are at risk not only of permanent systemic inflammation, but also of respiratory tract damage with subsequent narrowing, which should be the subject of increased attention to the prevention and safety of welding fumes containing zinc and/or copper [10, 13].

Various chronic consequences such as pulmonary fibrosis, bronchiolitis, bronchiectasis and other bronchial lesions can sometimes be observed as a result of acute injury, depending on the severity of the initial injury and treatment. In addition, even in the absence of structural complications after inhalation injury, a state of persistent non-specific bronchial hyperreactivity may persist. This variant of adult non-allergic asthma has been termed «reactive airway dysfunction syndrome» or «acute irritation-induced asthma» [3]. There have been isolated cases of severe MFF with the development of acute respiratory failure and death [17, 31].

Prevention

To prevent the occurrence of inhalation fever, adequate occupational hygiene should be ensured [3, 4]. Metal vapour concentrations in the workplace should not exceed the maximum allowable concentrations [17]. The USA, UK, Australia, Canada, Germany, the Netherlands, Sweden and Denmark have occupational exposure limits for ZnO of 5–10 mg/m^3 [4].

Melting of non-ferrous metals should be carried out in enclosed electric furnaces with maximum mechanisation of metal pouring and effective supply and exhaust ventilation. The most effective measure to prevent exposure to zinc fumes is a welding fume extraction system, including a source trap and local exhaust ventilation.

Workers and artisans should keep their heads and faces away from vapour and avoid inhaling them. Workers should wear appropriate protective masks and clothing [8]. A certain number of MFF cases occurred in workers who did not wear respirators [23], but the symptoms of metal fume fever disappeared after they wore a protective mask during welding [30]. Facepiece respirators have become a practical means of reducing inhalation exposure to metal particles in the workplace because they are lightweight and easy to use [8, 38–40]. To prevent the onset of a feverish process after work, it is recommended to take a warm shower [17, 31]. Occupational health education can help prevent metal fume fever at home, school and work [22].

Thanks to gradual improvements in workplace health, safety and exposure control over the past 100 or so years, there has been a significant decline in reported cases of metal fume fever [18, 29].

Conclusions

1. Metal fume fever is an occupational disease.

2. Inhalation of metal aerosols can cause tachyphylaxis.

3. In most cases, MFF is benign, but in some severe cases, the syndrome can be life-threatening.

4. Ensuring adequate occupational health is an effective way to prevent MFF.

5. Inhalation poisoning with heavy metals and MFF are different pathological conditions with different treatment in terms of pathogenesis, course, clinical manifestations and treatment.

The authors hope that this information will be useful to first contact physicians, general practitioners, intensive care specialists, occupational pathologists, pulmonologists and occupational and district therapists.

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Лихоманка парів металів (огляд). Частина II

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Анотація. В основі патогенезу лихоманки парів металів (ЛПМ) лежить неспецифічна неалергічна активація макрофагів або легеневих епітеліальних клітин із локальним і системним вивільненням пірогенних хемотаксичних медіаторів. Це підтверджується збільшенням кількості запальних цитокінів і білків гострої фази на початку ЛПМ. Інтерлейкін-6 є раннім високочутливим біомаркером впливу парів металів, що містять цинк і мідь. Частинки оксиду або вивільнені металопротеїнази матриці діють як алергени, або оксид цинку діє як гаптен і з'єднується з білком, утворюючи повний антиген. Існує 17 основних симптомів ЛПМ, і наразі не існує специфічного тесту для її діагностики. Варіанти лікування обмежуються симптоматичним полегшенням, включаючи анальгетики, нестероїдні протизапальні препарати та саліцилати, антациди та антигістамінні препарати, бронходилататори та, якщо необхідно, серцево-судинні препарати, кисневу терапію та лужні інгаляції. При тяжких синдромах зі зниженим насиченням киснем початковим лікуванням є назальна високопотокова киснева терапія. У більшості випадків прогноз позитивний із швидким і повним одужанням протягом 12–48 год після припинення впливу пари металу. Щоб запобігти розвитку ЛПМ, слід підтримувати адекватну гігієну на виробництві.

Ключові слова: лихоманка парів металів, патогенез, клініка, лікування, прогноз, профілактика.

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