Severe Hypersensitivity Dermatitis and Liver Dysfunction Induced by Occupational Exposure to Trichloroethylene

Xinyun XU1*, Rongxing YANG1, Nan WU1, Ping ZHONG1, Yuebin KE1, Li ZHOU1, Jianhui YUAN1, Geyi LI1, Haiyan HUANG1 and Bin WU1

1Department of Toxicology, Shenzhen Center for Disease Control and Prevention, 21 Tianbei Road, Shenzhen 518020, Guangdong, China

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Abstract: Trichloroethylene-induced hypersensitivity dermatitis is one of the serious occupational health events in China, however, little is known about the clinical features and possible mechanism of this disorder. The objective of the present study was to report some typical trichloroethylene-induced dermatitis patients and investigate their occupational exposure as well as the clinical features. We sampled and tested some cleaning agents from the companies where TCE-induced skin disorder occurred, the trichloroethylene concentrations were also monitored in the workplace air. Additionally, the symptoms, signs and laboratory test results of patients were collected. TCE concentrations varied from 10.2% to 91.4% in the cleaning agent by gas chromatography-mass chromatography analysis, and TCE levels in the workplace air ranged between 18 mg/m³ and 683 mg/m³, at most sampled sites TCE levels were higher than China national health standard for TCE. The trichloroethylene exposure time of the patients was 5–90 days (average 38.2 d), the patients with headache, dizziness, skin itch, fever were 90.5%, 100%, 100%, and 61.9%, respectively. 85.7% patients had skin erythema, 90.5% with rashes, and 38.1% with blisters. In addition, liver enlargement occurred in 3 patients, the abnormal rate of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T-Bil) were 90.5%, 85.7% and 76.2%, respectively. 6 out of 15 patients were with abnormal electrocardiogram, and trichloroacetic acid (TCA) elevated in 14 patients (66.7%). Taken together, the major detrimental effect of trichloroethylene was to induce hypersensitivity dermatitis and liver dysfunction, the occurrence of this disorder is likely related to the individual hypersensitivity to trichloroethylene exposure.

Key words: Trichloroethylene, Occupational exposure, Hypersensitivity, Dermatitis, Liver dysfunction

Introduction

Trichloroethylene (TCE) is one of the common organic solvents which is widely used in metal degreasing and cleaning, it is principally applied in those industries such as electronic company, printing company, electroplating company or hardware company. It has been reported that TCE had various toxicities and could induce skin damage, liver damage, even heart or kidney impairment1–3). In recent years we found that some workers exposed to trichloroethylene suffered from hypersensitive dermatitis, we usually named this disease the TCE-induced dermatitis or TCE-induced hypersensitive disorder, but some researchers named it the TCE-related generalized skin disorder, or TCE-related hypersensitivities or TCE-induced medicamentosa-like dermatitis which resemble drug hypersensitivities4–6). These TCE-related hypersensitivities are different from typical solvent toxic effects in terms of unclear dose-response relationship, period of exposure before disease onset, generalized rash, fever, and recurrence just after minimal re-exposure7–8). The num-
ber of cases reported with these occupational skin disorders or subsequent death has been increasing after the mid-1990s in China\(^9\). Recently TCE-induced hypersensitive disorders have become one of the serious occupational health events in China, however, the disorders have not drawn much attention worldwide. Furthermore, the mechanism by which TCE induced hypersensitive dermatitis and liver dysfunction even patient’s death remains unclear.

In the present study we investigated 21 patients with TCE-induced dermatitis, and analyzed their job type, TCE exposure time, their major symptoms, physical signs as well as the laboratory test data so that we could understand the clinical characteristics of this disorder, and provide scientific evidence for research on mechanism or preventive measurements of TCE-related hypersensitive dermatitis.

**Subjects and Methods**

*Subjects*

This study was conducted with local ethics authority approval and patient consent. 21 typical patients with TCE-induced skin disorder were investigated during the year of 2003 and 2005 in Shenzhen city in south China, 8 of them were male, and 13 were female, their average age was 21.3 ± 1.8 yr old. Among 21 patients 5 worked in the electronic company, 11 in hardware product factory, 2 in electroplating company, and the remained 3 patients in other kind of industry.

*TCE exposure investigation*

The patients were exposed to TCE through applying TCE to clean or degrease metal products or electronic products, usually they use TCE by their hands without wearing rubber gloves, so the possible pathways for TCE entrance to the human body included the respiration and skin contact. The duration of TCE exposure among these patients varied in individuals, the shorter exposure was 5 d, and the longer was 90 d, the average was 38.2 d.

Usually when any case of TCE-induced skin disorder occurred the TCE exposure levels were investigated. We sampled and tested some cleaning agent from the companies where TCE-induced skin disorder occurred. We investigated and sampled the cleaning agents from 4 companies where TCE-induced skin disorder occurred, the data showed that the cleaning agents contained TCE, the TCE concentrations in 4 samples were 10.2%, 37.5%, 91.4% and 63.5%, respectively. Additionally, the purity of TCE in the solvents was detected with gas chromatography -mass chromatography, it was found that the impurities of the solvents composed of acetone, toluene, xylene, butyl acetate and water. TCE levels in the workplace air were also determined with the method of area monitoring for 8 h according to the China national health standard “specifications of air sampling for hazardous substances monitoring in the workplace (GBZ159–2004)”\(^1\). The airborne samples were usually collected with the air samplers that was manufactured by Jianhu electronic company in Jiangsu province in China, and the air sampler type was TWA 300. We collected the airborne samples in the areas where the patient with TCE-induced skin disorder worked. 3 to 4 samples were taken for determination of TCE levels at any company where TCE hyper-sensitivity dermatitis occurred. The TCE concentrations expressed as a time-weighted average (TWA) in the workplace air varied between 18 mg/m\(^3\) and 683 mg/m\(^3\). We found that 6 patients in 6 factories were exposed to lower TCE levels (17.6 ± 7.4 mg/m\(^3\), the average ± the standard deviation) than the occupational exposure limit 30 mg/m\(^3\).

*Clinical data collection*

When the workers exposed to TCE suffered from the TCE-induced skin disorder, we investigated the cases and recorded the patient’s symptoms and signs. As the center for disease control and prevention, we also asked the hospitals where the patients were given medical treatment to provide us with some laboratory test data of the patients so that we could conduct the diagnosis for the patients. In this article the laboratory test data included ALT, AST, total bilirubin, urinary TCA, and ECG test.

Urine samples were collected for determination of trichloroacetic acid (TCA, the metabolite of trichloroethylene). Usually when the TCE-induced skin disorder occurred the urine samples were collected immediately from the patients, the latency between the last TCE exposure and the urine collection varied from 2 d to 4 d.

*Results*

*TCE levels in the workplace air and TCE purity of solvents*

We investigated and sampled the cleaning agents from 4 companies where TCE-induced skin disorder occurred, the data showed that the cleaning agents contained TCE, the TCE concentrations in 4 samples were 10.2%, 37.5%, 91.4% and 63.5%, respectively. Additionally, the purity of TCE in the solvents was detected with gas chromatography -mass chromatography, it was found that the impurities of the solvents composed of acetone, toluene, xylene, butyl acetate and water. TCE levels in the workplace air were also determined with the method of area monitoring for 8 h according to the China national health standard “specifications of air sampling for hazardous substances monitoring in the workplace (GBZ159–2004)”\(^1\). The airborne samples were usually collected with the air samplers that was manufactured by Jianhu electronic company in Jiangsu province in China, and the air sampler type was TWA 300. We collected the airborne samples in the areas where the patient with TCE-induced skin disorder worked. 3 to 4 samples were taken for determination of TCE levels at any company where TCE hypersensitivity dermatitis occurred. The TCE concentrations expressed as a time-weighted average (TWA) in the workplace air varied between 18 mg/m\(^3\) and 683 mg/m\(^3\). We found that 6 patients in 6 factories were exposed to lower TCE levels (17.6 ± 7.4 mg/m\(^3\), the average ± the standard deviation) than the occupational exposure limit 30 mg/m\(^3\).
which was recommended by the ministry of public health of China (Occupational exposure limit for hazardous agents in the workplace, GBZ2-2002, China). The other 15 patients in 15 factories were exposed to higher levels of TCE (45.7 ± 13.5 mg/m³) than the China national health standard.

**Major symptoms and skin lesions of patients with TCE-induced disorder**

After the workers were exposed to TCE for 2 to 5 wk they usually have some symptoms, such as headache, dizziness, fever, then skin itch of arms or legs or whole body, fatigue, anorexia, nausea, vomiting. In the serious individuals sleep or coma even death occurred. In this study we could find the higher positive rate of headache, dizziness, fatigue, nausea, appetite decrease, and skin itch. 13 out 21 patients had high temperature, the highest temperature was 39.2°C, and the average temperature among 21 patients was 37.8°C.

The principal sign of patients with TCE-induced dermatitis was the skin damage. In the early stage the patients usually had skin changes in face, neck, arms or legs, including scarlet skin, erythema, rash, these changes got worse and worse after 3 or 4 d (Figs. 1 and 2). The patients’ face and eyelid were swollen, the lips and mucous membrane of mouth exuded, consequently the patients opened their mouth with hardness, could not ingest food easily. Except scarlet skin, erythema and rash, the skin blisters also occurred in a part of patients, sometimes several blisters combined together, the blisters then broke, exuded, scabbed, finally the scarfskin necrotized and fallen off. Among the patients approximately 80% to 90% had obvious skin impairment, such as scarlet skin, rash, erythema, and blisters. Additionally, jaundice and liver enlargement occurred in some patients. See Table 1.

**Laboratory test**

ALT, AST and T-Bil were tested in 21 patients, the abnormal rates of the above test were 90.5%, 85.7% and 76.2%, respectively. The routine blood tests were conducted in all patients, WBC increase was found in 5 of them. The urinary protein was positive in 2 patients. 15 patients were conducted with ECG test, and 6 of them had abnormal ECG (4 patients with sinus arrhythmia, one patient with sinus bradycardia and one patient with sinus tachycardia). Trichloroacetic acid (TCA), the metabolite of TCE, was measured in 21 patients (Table 2). It was found that TCA in 14 patients was higher than 50 mg/l, the recommended value by the ministry of public health of China. The highest level was 90.8 mg/l.

<table>
<thead>
<tr>
<th>symptoms and signs</th>
<th>positive patients</th>
<th>positive rate (%)</th>
<th>symptoms and signs</th>
<th>positive patients</th>
<th>positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>headache</td>
<td>19</td>
<td>90.5</td>
<td>fever</td>
<td>13</td>
<td>61.9</td>
</tr>
<tr>
<td>dizziness</td>
<td>21</td>
<td>100</td>
<td>scarlet skin</td>
<td>17</td>
<td>80.9</td>
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<tr>
<td>fatigue</td>
<td>18</td>
<td>85.7</td>
<td>rash</td>
<td>19</td>
<td>90.5</td>
</tr>
<tr>
<td>nausea</td>
<td>15</td>
<td>71.4</td>
<td>erythema</td>
<td>18</td>
<td>85.7</td>
</tr>
<tr>
<td>vomiting</td>
<td>11</td>
<td>52.3</td>
<td>blisters</td>
<td>8</td>
<td>38.1</td>
</tr>
<tr>
<td>appetite decrease</td>
<td>18</td>
<td>85.7</td>
<td>jaundice</td>
<td>7</td>
<td>33.3</td>
</tr>
<tr>
<td>skin itch</td>
<td>21</td>
<td>100</td>
<td>liver enlargement</td>
<td>3</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Table 1. The major symptoms and signs in 21 patients with hypersensitivity dermatitis.

![Fig. 1. Erythema multiforme, epidermal necrolysis, and maculopapular eruption occurred on the back of the patient with trichloroethylene-induced hypersensitivity dermatitis.](image1)

![Fig. 2. Cutaneous manifestations on upper trunk of the patient with trichloroethylene-induced dermatitis. Erythoderma, maculopapular eruption, exfoliative dermatitis and desquamation developed.](image2)
Discussion

TCE has been applied in industry for a long time, and there are a lot of studies about TCE toxicity. It is reported that TCE can inhibit nervous system, it can also produce harmful effects on the liver, kidney, heart and skin. In recent years some researchers found that TCE was one of carcinogens, and IARC listed TCE as the carcinogen in group 2A\(^{10}\).

Skin damage is the most typical clinical feature of TCE-induced disorder, which can be classified into four categories: exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, and epidermolysis bullosa\(^7, 10\) or toxic epidermal necrolysis\(^11\). To some extent TCE-induced skin disorder is similar with drug-hypersensitivity dermatitis, cutaneous manifestations usually begin as a morbilliform eruption; the face, upper trunk, and upper extremities are the first body parts to be affected and then followed by the lower extremities; erythroderma may occur, and the maculopapular eruption later becomes infiltrated and indurated; another clinical presentation is mucosal involvement.

Although the symptoms varied in severity, however the symptoms appeared similarly. The patients usually have headache, dizziness, fatigue, fever, and skin itch. Because these symptoms lack specificity, it is uneasy to make right diagnosis at the early stage. Skin damage is the dominant signs, the present study indicated that most patients had scarlet skin (80.9%), erythema (85.7%) and rash (90.5%), in serious patients the skin blisters come out. This kind of skin damage usually appeared 3–4 d after the dermatitis occurred, it starts from the face, then extends the neck, arms and trunk. It should be noted that TCE-induced skin damage is different from the contact dermatitis which happened on the local area where chemicals were exposed directly. Therefore we think that the skin damage is a valuable factor for diagnosis of TCE-induced hypersensitivity dermatitis that is considered as a kind of occupational disease in China.

Besides the skin disorder, TCE also induced obvious liver dysfunction in some patients, the patients had jaundice, liver enlargement, elevated bilirubin, ALT increase and AST increase\(^6, 7, 12\). In this study the rate of ALT, AST and total bilirubin elevation was 90.5%, 85.7% and 76.2%, respectively. During 1990’s to early 2000’s the mortality was around 20% or even higher in TCE-related dermatitis patients in China, liver failure, infections, and the resulting sepsis were the principal causes of mortality\(^4, 13, 14\). A few patients with TCE-related skin disorders reportedly died from serious liver dysfunction, or from gastrointestinal bleeding and the resulting disseminated intravascular coagulation\(^15\). The liver dysfunction observed in TCE-related skin disorders was non-viral and apparently different in its clinical course from usual TCE-induced hepatitis, which occurs without showing rash at high concentrations in direct relation to P450-derived metabolites\(^16, 17\). With regard to hepatitis (here it means liver damage instead of viral hepatitis), Xia reported that 94% of patients of the TCE-related skin disorders in China had suffered from hepatitis\(^11\).

Some reports indicated that heart is probably another target organ of TCE, TCE could induce irregular heartbeat, S-T change, or myocardial disease\(^6\). Among 15 patients with ECG test in this study, 6 of them had abnormal ECG, suggesting heart toxicity of TCE should not be neglected.

One of the principal TCE metabolites is trichloroacetic acid (TCA), which is a specific index for TCE absorption. Although TCA levels can’t represent the severity of TCE-induced disorder, it is helpful for making right and timely diagnosis of dermatitis induced by TCE. It should be noted that TCA has half time of excretion, which is about 2–5 d\(^18, 19\). If any persons who are exposed to TCE and with hypersensitivity dermatitis are found, the urinary TCA level should be measured within 5 d after the cessation of exposure to TCE, or else the measured TCA concentration could be a trace level.

According to the occupational exposure, the patient’s symptoms and signs as well as laboratory test, we summarized the following features for TCE-induced skin disorder: 1. only a few of workers who were exposed to TCE suffered from the hypersensitive dermatitis, namely, the incidence of TCE-induced skin disorder was low. 2. all patients had a history of TCE exposure, most of them were exposed to TCE directly, but we found 2 patients were exposed to TCE indirectly in China, namely these two patients worked in the environment which was close to the workplace where TCE was applied. 3. there was no dose-

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Table 2. TCE exposure time and laboratory test results in 21 patients with hypersensitivity dermatitis

<table>
<thead>
<tr>
<th>TCE exposure time (d)</th>
<th>Temp (˚C)</th>
<th>ALT (U/l)</th>
<th>AST (U/l)</th>
<th>T-Bil (mg/l)</th>
<th>U-TCA (mg/l)</th>
<th>ECG*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>5–90</td>
<td>36.8–39.5</td>
<td>29–2,167</td>
<td>23–983</td>
<td>14.6–62.8</td>
<td>15.2–90.8</td>
</tr>
<tr>
<td>Mean</td>
<td>38.2</td>
<td>37.8</td>
<td>497.2</td>
<td>128.2</td>
<td>30.3</td>
<td>52.5</td>
</tr>
<tr>
<td>SD</td>
<td>18.3</td>
<td>0.9</td>
<td>532.5</td>
<td>202.6</td>
<td>13.8</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Note: *ECG was tested in 15 patients, 4SA means 4 patients with sinus arrhythmia (SA), 1SB means one patient with sinus bradycardia (SB), 1ST means one patient with sinus tachycardia (ST). *SD means standard deviation.
response relationship between TCE exposure and hypersensitivity dermatitis\(^{12}\), this means that the severity of disorder doesn’t matter with TCE exposure levels. 4. the latency period varied from a few days to a few months, the shortest latency is 5 d, but the longest is 3 months. 5. almost all patients had fever, usually the temperature was around 38°C, but sometimes the high fever around 40°C could be seen. 6. skin damage was the typical clinical feature, most patients have skin lesion including scarlet skin, erythema and rash, etc. 7. liver dysfunction occurred in most patients with TCE-induced skin disorder, the enzyme activities of ALT and/or AST increased to 1,000 U/l, or even higher levels. 8. male and female workers exposed to TCE had equal chance to suffer from TCE-related dermatitis. Additionally, the patients with TCE-related dermatitis were found to be at every stage of ages. 9. urinary TCA was higher than 50 mg/l in more than half of the patients, but TCA levels didn’t represent the severity of TCE-induced disorder. 10. the TCE-induced disorder could reoccur when patients re-exposed to TCE. 11. patch test could be positive in some patients when TCE or its metabolites were used in the test. 12. glucocortcoids therapy was effective in most cases\(^{20}\).

Some researchers have explored the mechanism of TCE-induced skin disorder in recent years, but the mechanism remains unclear. Li and his colleagues\(^{21, 22}\) studied the allergenic activity of trichloroethylene and its three metabolites (trichloroacetic acid, trichloroethanol and chloralhydrate) by using guineapigs as the experimental subjects. 2,4-dinitrochlorobenzene was used as the positive control, edema and erythema were observed as the allergic indexes, the results showed that the allergenic rates of trichloroethylene, trichloroacetic acid and 2,4-dinitrochlorobenzene were 71.4%, 58.3% and 100%, respectively, but trichloroethanol and chloralhydrate did not induce edema and erythema. Dai\(^{23}\) reported that IgG level in serum of TCE-sensitized guineapigs was significantly higher than that in normal animals, no obvious differences in splenic T lymphocytes proliferation index and NK cell activity between TCE-sensitized and normal guineapigs were found. Some authors reported that TCE-induced skin disorder could be associated with the factors such as TNFα gene polymorphism\(^{24}\), P450 metabolism enzyme gene expression\(^{25}\), enzyme gene polymorphism of aldehyde dehydrogenase and alcohol dehydrogenase\(^{26}\). Haishan Li\(^{27}\) found that the allele HLA-B*1301 was strongly associated with TCE-induced hypersensitivity dermatitis among exposed workers and might be used as a biomarker to predict high risk individuals to TCE. Hanlin Huang and his co-researchers reported human herpesvirus 6 was reactivated in patients suffering from TCE-induced hypersensitivity dermatitis\(^{28}\). Since the finding was analogous with that observed in severe drug hypersensitivity\(^{29}\), it demonstrated the possible involvement of human herpesvirus 6 in TCE-induced hypersensitivity dermatitis. Additionally, other authors found some factors such as polymorphisms of human leucocyte antigen DRB1 genes, lymphocytes, cytokines, polymorphisms of aldehyde and alcohol dehydrogenase genes, could be associated the TCE-induced skin disorder\(^{30–33}\). Based on these findings, it seems that the mechanism of TCE-induced skin disorder is likely related to the individual hypersensitivity to trichloroethylene exposure and need further study. To our knowledge we think the mechanism of TCE-induced skin disorder is quite complicated, we suggest that much more attention should be drawn by the scientists in the field of biochemistry, molecular biology, genetics, immunology, toxicology, occupational medicine, and the worldwide cooperation will be helpful in exploration of this complex problem.

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References