1. Background

This report was prepared according to reports published in the literature and information of Levamisole (LMS) supplied by Rong-yuan Zheng Research Group in the first affiliated hospital of Wenzhou Medical College on March 2005. Chinese biomedicine bibliographic database (CBMdisc), Chinese journal full-text data base (CNKI), MEDLINE, network station of SFDA other network stations) have been searched.

Levamisole is firstly developed by Jassen pharmaceutical LTD. in Belgian. It has been used for killing and debugging parasite with broad-spectrum and activating immune function. After putting on the market in 1970’s, LMS was generally considered as “more efficient, broad-spectrum and safe” anti-parasite miracle drug. For more than 20 years, it had been extensively used in clinical application and selected as essential anthelmenthic in China and many other countries. It was not only used as anti-helminth infection drug to treat ascariasis, enterobiasis and ancylostomiasis, but also used as an immunoenhancer for anti-malignant tumor combined chemotherapy, for example LMS treated cancer of colon combined with fluracil. In addition, it was used as immunomodulator to treat dysimmunity disease, such as alopecia, facial plana-verruca, subsepsis allergica, chronic tracheitis, anabrotic intestinal tract disease, arthritis deformans, nephrotic syndrome and so on.

Following clinical using experience for 20 years, it is gradually discovered that LMS had several severe adverse drug reactions (ADRs) which referred to several systems and organs all over the body. One is “cute demyelinating encephalopathy induced by Anthelmintic Imidazoles, ADEIBAI”, which is also known as the drug related “encephalitis syndrome”, “delayed encephalopathy”, “allergic leuco-encephalitis/allergic leukoencephalopathy” or “drug-induced encephalopathy”.

2. Severe ADR Reports of LMS

“ADEIBAI” caused by LMS was first reported by Rong-yuan Zheng et al. in 1985[1]. Later on, a lot of similar cases were found in China. The outcome is very serious, mortality rate is 7.5%, morbidity rate is 50.3%. Although incidence of the LMS-induced ADEIBAI is not high, which is 45.8/100 thousand according to the scene investigation in Wenzhou in 1988 [2], the total cases of ADEIBAI is not a small
amount as China is a big country with big population.

Up to now, 632 severe cases related to neural system have been reported in China, shown in table 1. Thereinto, 543 cases are ADEIBAI.

**Table 1. Severe ADRs caused by LMS in nervous system reported in China**

<table>
<thead>
<tr>
<th>Severe ADRs in neural system</th>
<th>Case number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>632</td>
</tr>
<tr>
<td><strong>ADEIBAI</strong></td>
<td>543</td>
</tr>
<tr>
<td><strong>other severe ADRs</strong></td>
<td>89</td>
</tr>
<tr>
<td>epileptic seizure</td>
<td>26</td>
</tr>
<tr>
<td>ataxia</td>
<td>21</td>
</tr>
<tr>
<td>dysarthria</td>
<td>14</td>
</tr>
<tr>
<td>extracorticospinal tract symptom</td>
<td>4</td>
</tr>
<tr>
<td>tetrican ankyloideire</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonian syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Acute demyelinating myelopathy</td>
<td>1</td>
</tr>
<tr>
<td>vision damage(optic neuritis)</td>
<td>15</td>
</tr>
<tr>
<td>dysaudia</td>
<td>4</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

All data from Chinese journal full-text data base (1994 to 2003, patients with defined history of medication)

The reported ADEIBAI cases caused by LMS were found all over the country. According to some clinical records, it is found that thirty-five reports were from twenty-four Medical Therapy Units, the patients came from 8 provinces, and more than 10 cities.

The indication of LMS in China: most patients took LMS as an anthelminthic which was used to treat ascariasis, ancylostomiasis and enterobiasis; a few patients took LMS as immunomodulator which was used to treat alopecia, facial plana verruca, subsepsis allergica, chronic tracheitis, rheumatoid arthritis, nephrotic syndrome, etc.

Severe ADRs in nervous system reported from other countries in the world was added up to 28 cases. Of them, there were twenty-three cases of ADEIBAI (two cases were monotherapy with LMS alone, twenty-one cases were treated by LMS in combination with 5-FU), and other severe ADRs in neural system were five cases which were dystaxia, progressive dementia, psychinosis-like symptom, epileptic seizure, optic neuritis, respectively.
In 1992, it was beginning to report the ADEIBAI in other seven countries, involving America, Germany, Italy, France, Japan, British, Vietnam.

The indications in these countries was obviously different from China. LMS was taken as an adjunctive therapy to enhance the immunity of patients who had colon carcinoma, mammae carcinoma, melanotic cancer, nephrotic syndrome, Crohn's disease, rheumatoid arthritis, etc.

Severe ADRs caused by LMS out of neural system: eighty-four cases were reported from China. The main of them were influenza-like syndrome, allergic erythra, allergic shock, acute agranulocytosis.

3. Clinical features of ADEIBAI in China

(1) Acute or subacute onset.

(2) With a history of taking anthelmintic imidazoles 2-5 weeks before onset of the disease (A few patients might show up immediate ADRs at the day of administering drug or the next day. These ADRs were influenza-like syndrome with headache, nausea, fever, myasthenia of limbs, or urticaria-like erythra lasting 1-7 days)

(3) Main symptoms and signs: no fever; severe mental disorders in early stage; diffuse multifocal neurological disorders at progressive stage. (gradually appearing the manifestation of serious ADEIBAI 10-40 days after taking LMS: the initial symptoms such as speech reduction, mutism or hypokinesia, apathy, inhibition of thinking, memory loss and sharp reduction of calculation, followed by the nervous symptoms of the diffuse damaged: dizziness, headache, weak ambulation, seizure, urinary and fecal incontinence, hemiplegia, quadriplegia etc., and conscious disturbance in some patients: somnolence, lethargy and coma; findings in physical examination: hypo-myodynamia, hypermyotonia, hyperreflexia, and positive pathologic reflex).

(4) Auxiliary examination: Electroencephalogram(EEG): midrange to Severe abnormal EEG found in more than 90% patients, with predominant slow wave; Examination of cerebrospinal fluid(CSF): normal in half cases or mild inflammatory change and increased amounts of IgG; Cranial CT: the extensive lamellar or multifocal plaquelike low density shadow in brain; MRI: multiple white matter lesions signal, unusually round-like in shape with long T1W and long T2W; Biopsy of brain: Pathological examination with light microscope: the infiltration of inflammatory cell and demyelination in the area of lesions, electron microscope: disintegration, disjunction and defluxion of myelin sheath with the pathologic characteristics of acute multifocal inflammatory leukoencephalopathy, or of acute allergy encephalitis.
Clinical types: the mental abnormal type, the hemiplegia type, the coma type, the pseudoneoplasm type, and the benign intracranial hypertension type.

Monophase self-limited course of the disease: if the patient re-taking LMS at the second time within an interval of months or years who could be induced the relapsed encephalopathy reoccurred the manifestations similar to that of the ADEIBAI at the first time. The relapse ratio of the ADEIBAI was 8.4%.

Treatment and outcome: Certain therapeutic effect of corticosteroids could be found in the treatment of this disease with fatality rate 7.5% at acute stage, The duration of disease is ranged 3 to 6 months, they would have a better long-term rehabilitation with recovery rate of 78.0% and improvement rate of 10.0%, respectively.

4. The characteristics of epidemiologic distribution of ADEIBAI in China

4.1 Region distribution:

The geographic distribution of 193 cases of the ADEIBAI in Wenzhou city showed: The incidence rate in 4 counties along near two rivers (the Oujiang river and the Feiyun river) was two to five times than that in other 5 counties far away from rivers. The investigation found out: nonprofessional physician, folk doctors, had been engaged in the activity of saling antihelmintic (LMS) at the several ferry boats on the two rivers over the years. Partial patients who took LMS themselves suffered from the ADEIBAI [3].

4.2 Time distribution

It was sporadic in the whole year without epidemic outbreak. There was no seasonal fluctuation and clustered distribution. There was a curve with presenting two epidemic high peaks and an epidemic low valley according to the investigation in Wenzhou area. The former, two peaks, was concerned with TMS and LMS on the market, the latter, one valley, was an outcome of the intervention effect of withdrawing TMS from the market.

4.3 Population distribution:

The incidence was not related to occupation, residential belt. The age of onset ranged from 4 years old to 62 years old with the average 33.6 ± 10 years olds( mean age: 35 years old). The percentage of 16-44 years old patients was 91.1%. Female had much higher susceptibility than male, the ratio was 0.65. The fourteen cases with manifestation of intracranial hypertension were all female.
4.4 Exposure of the drug

Most patients took the routine dose (150mg—300mg), using peroral administration, or besmearing on the skin with 1 or 2 times. There was no overdose and cumulative poisoning. Most of patients took LMS at night and in the next early morning on an empty stomach without concomitance of any other drug or any food. So it could be excluded the interaction with other drugs or foods.

Source of the drug: according to the recording of partial cases in Wenzhou, 22% of the exposed drug was bought from pharmacy or drugstore, 75.5% identified as LMS was bought from nonprofessional physician, “folk doctors”, 0.5% was distributed for universal cure (mass treatment). The drugs were productive of 17 different corporations, 17 disparate places and had more than 10 batch number.

Effect and side effect after exposure: only 23.9% of patients had the effect of anthelminthic and others didn’t have worms drove, it is suggested that there is not a close relationship between the disease and the effect of anthelminthic. The incidence of early immediat ADRs was 56.7%, which emerged from a few hours at the day or the next day after taking LMS and lasted on 1—5 days. The incidence of the delayed ADRs was 8.9%, which were hepatitis-like response (4.7%), hematonosis-like response (2.2%), agranulocytosis, granulocytopenia, thrombopenic purpura and oral ulcer, etc. The incubation period of the delayed ADRs was 1—6 weeks and the duration was 1—3 weeks.

5. References with abstract:

[1].

The primary research on experimental allergic encephalomyelitis induced by levamisole in rats  Li Yong*, LI Jian-min, ZHENG Hong-yan, et al. * Department of Neurology, the First Affiliated Hospital, Wenzhou Medical College, Wenzhou 325000

Abstract: Objective: To observe the effect of experimental allergic encephalomyelitis induced by levamisole in rats.

Methods: Fifty Wistar rats were randomly divided into five groups: control group, guinea pig spinal cord homogenate (GPSClH) plus complete Freund's adjuvant (CFA) group, levamisole group, levamisole plus CFA group and CFA group. The diet, movement, body weight of Wistar rats were daily examined, CNS tissues were stained with hematoxylin-eosin and lead fast blue. Results: 1 Two of ten rats in levamisole plus CFA group and five of ten in GPSClH plus CFA group demonstrated neurological signs of typical EAE, with parenchymal infiltration and perivascular cuffing with mononuclear cells, and demyelination in the white matter. 2 Eight of ten in CFA group demonstrated the signs of the adjuvant arthritis, without demyelination and infiltration of mononuclear in CNS. 3 No infiltration of mononuclear and myelin damages in CNS were noted in all rats of LMS and control groups. Conclusion: Levamisole plus CFA can directly induce EAE in wistar rat.

The results of a cohort study of 92,346 labour population for probing the relationship between levamisole (LMS) and encephalitis syndrome was reported. There were five patients suffering from the disease in an exposed group (E) of 10,911 people within two months after taking LMS as an anthelmintic for mass treatment, the incidence of the disease is 4.58/10,000. The nonexposed population was divided into two control groups the first group (N1) includes 37,990 people living in the mass treatment villages and the other group (N2) consists of 43,445 people living in the adjoining villages without mass treatment. None in the two control groups suffered from the syndrome or any other encephalitis-like disease within the same period. Statistical tests for the differences between E and either N1 or N2 separately is highly significant. (between E and N1: $P = 0.000553, P < 0.001$; between E and N2: $P = 0.000325, P < 0.001$). The overall attributable risk (AR) is 45.8/100,000 and that for female is 93.8/100,000. However, the difference between the incidence rates of the disease in female and male is not statistically significant ($P > 0.025$). It is shown that LMS is obviously the causative factor of the disease.