Autoimmune hypoglycemia, also called insulin autoimmune syndrome (IAS), was first reported by Hirata and Ishizu in 1972 in Japan. IAS is characterized by the diagnostic criteria of spontaneous hypoglycemia without evidence of exogenous insulin administration, high levels of total immunoreactive insulin, and the presence of a high titer of insulin autoantibodies. IAS is listed as the third largest cause of spontaneous hypoglycemia, gradually drawing people's attention. From 1970 to 2013, the global spontaneous hypoglycemia caused by IAS was more than 400 cases with cases occurred in Asia. Since 1970, in Japan over 200 cases of IAS were reported, only a few cases were reported outside Asia. Since the first reported by Xiang et al. in China, with the improvement of diagnostic methods, the Mainland of China also have relevant case reports. IAS can be easily missed and misdiagnosed, the prevalence of IAS is also difficult to estimate. So far the largest epidemiological study worldwide about IAS was conducted by Uchigata in Japan, a retrospective study collecting epidemiological characteristics and clinical features. However, there is no large-scale epidemiological investigation of IAS in China. In this study, we investigated the characteristics of 73 patients with IAS obtained through a nationwide questionnaire survey.

These patients were diagnosed with IAS from 1985 to 2013 based on the criteria of Hirata. We collected the following clinical information of each IAS patient: the age at onset, sex, duration of hypoglycemic attacks, outcome or treatment, medication taken prior to the onset of IAS and background disease. However, almost all patients had been detected with high concentrations of insulin and related antibodies.

The ages at onset varied widely, peaked at 60–69 years old for male but 30–39 years old for female. There was no remarkable sex difference across different age groups except the 30–39-year group, in which 85% were females. In terms of hypoglycemic attacks, 16 of 33 (48%) male and 18 of 40 (45%) female patients had duration of less than 1-month. 12 of 33 (36%) male and 13 of 40 (32%) female patients had duration of more than 1-month but less than 3 months. Five patients had mild hypoglycemic attacks continued for more than one year. No remarkable sex difference was showed in the different duration. As shown in Table 1, 64 patients had taken medication prior to the onset of IAS: 47 IAS patients had Graves’ disease and had been treated with methimazole (MTZ) or propylthiouracil. Four IAS patients had been treated with a-mercaptopropionyl glycine (MPG) for liver disease. Moreover, captopril for hypertension was given to two IAS patients. MTZ, MPG and captopril are all sulfhydryl compounds. Seven patients had taken nonsulphhydryl compounds, such as steroids for rheumatoid arthritis, diltiazem hydrochloride for hypertension, loxoprofen sodium, tolperisone hydrochloride and giclofenac sodium for lumbar pain. The patients had hypoglycemia after taking MTZ, MPG, and captopril. After such drugs were discontinued, the hypoglycemic attacks subsided.

In China, MTZ has often been used for the treatment of Graves’ disease, MPG for the treatment of chronic hepatitis. In this study, we found that not only MTZ but also methimazole (MPZ) could trigger the development of IAS. Although captopril has been one of the most common anti-hypertensive drugs in China, it is still unknown why captopril appeared to cause the development of IAS less frequently than MTZ or MPZ, there are two reports of histological studies of pancreas specimens from partial
pancreas excision surgery, one case of pathological tissue was not seen unusual, the other one showed hyperplasia of pancreatic islets and in which case chronic pancreatitis and various sized islets was shown. Besides the genetic predisposition, the development of this disease may also require environmental factors. Some IAS cases coincided with autoimmune disease, such as hyperthyroidism, followed by systemic lupus erythematosus, systemic sclerosis, acanthosis nigricans. Moreover, clear cause of some patients with IAS was not found. It is possible that sulfhydryl compounds such as MTZ, MPG might be responsible for the disease. The IAS patients who had taken MTZ and/or MPG prior to onset had spontaneous remission after stopping such medication. For patients who had no history of such medication prior to onset, it is difficult to determine whether they had or had not been exposed to any drugs or reagents containing sulfhydryl compounds. After treatment with drug, antibodies can be converted into negative with the development of the symptom.

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Conflicts of interest
There are no conflicts of interest.

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Table 1: Drugs taken before the onset of IAS in 73 patients with this disease

| Drug               | Associated disease | Male | Female | Total |
|--------------------|--------------------|------|--------|-------|
| MTZ                | Graves’            | 13   | 28     | 41    |
| PTU                | Graves’            | 4    | 2      | 6     |
| MPG                | Liver dysfunction  | 4    | 0      | 4     |
| Captopril          | Hypertension       | 1    | 1      | 2     |
| Alpha lipoic acid  | Diabetic peripheral neuropathy | 1 | 3 | 4 |
| Non-SH compounds   |                    | 4    | 3      | 7     |
| Total              |                    | 27   | 37     | 64    |

IAS: Insulin autoimmune syndrome; MTZ: Methimazole; PTU: Propylthiouracil; SH: Sulfhydryl; MPG: Mercaptopropionyl glycine.