Informed Consent Form

A Retrospective and Prospective Observational Study of Hyperthyroidism in Children

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You are invited to participate in this study because you are eligible for study enrollment in the retrospective and prospective study of hyperthyroidism in children. Your study doctor or researcher will fully explain the informed consent for you. Please read this informed consent carefully before making a decision on whether to participate in the study. If you are participating in another study, please inform your study doctor or researcher.

The content, risks and other important information of this study are as follows

1. Why did this study take place?

1.1 Research background

Hyperthyroidism is rare in children, with a frequency of 0.1-3.0 per 100,000[1]. Hyperthyroidism in children is mainly caused by Graves' disease (GD). The girl-to-boy incidence rate ratio is approximately 4:1[2]. At present, antithyroid drugs (ATDs) remains the primary choice for children with GD[2-5]. The guidelines strongly recommend that methimazole(MMI) should be used in children undergoing ATDs treatment[2-5]. The common side effects of MMI include cutaneous reaction, neutropenia, leukopenia, high transaminase levels, arthritis, etc[2]. Few studies focus intensively on the large subjects of adverse reactions following ATDs treatment in hyperthyroidism children, as most patients failed to follow up regularly, and the risk factors of adverse reactions were not investigated in depth. There are significant differences in research results[6-12].

In studies of adults, the incidence of leukopenia and agranulocytosis was approximately 1.3% and 0.1-0.3% respectively[13-15]. There is a scarcity of research on pediatric cohorts regarding this topic. A review summarized the occurrence of adverse reactions in children with hyperthyroidism treated with MMI, 17.6% of the patients underwent at least one adverse event[16]. The incidence of neutropenia/leukopenia and agranulocytosis was roughly 1.1% and 0.3% respectively. However, the studies included in this review were not systematic in the exploration of adverse reactions, and the diagnostic criteria and follow-up time of adverse reactions were not consistent, hence the incidence rate obtained might not be accurate.

In an earlier study, Sato et al. closely monitored 64 children with GD who were treated with MMI for 1 year and discovered that only 1 patient (1.6%) developed neutropenia[11]. Subsequently, Korean scholars also carried out relevant studies on 99 GD children and concluded that the incidence of neutropenia under MMI was approximately 9.1%. The incidence of neutropenia significantly rose with the increase in the initial dose of MMI[8]. In a Chinese study conducted a 12-week follow-up was carried out on 161 GD children, revealing that the incidence of neutropenia after MMI treatment was approximately 5.0%[12]. Recently, a study compared the occurrence of neutropenia in GD children treated with MMI (110 cases) and carbimazole (CBZ, 40 cases), and found that the incidence of neutropenia after MMI treatment was 16.5%. However, the patients in this study were followed up at longer intervals, which might result in missed diagnoses[17].

In summary, the current studies have several issues, including a small sample size, a short follow-up period, and long follow-up intervals, which cannot accurately reflect the occurrence of neutropenia after MMI treatment. Herein, we conducted a bidirectional cohort study with a large sample size and regular follow-up to further investigate the clinical features and risk factors for neutropenia after MMI treatment in hyperthyroidism children.

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1.2 Objectives of Study

This study intends to conduct a retrospective and prospective study on children with hyperthyroidism, and it is a non-intervention study to collect information on diagnosis and treatment and long-term follow-up of children with hyperthyroidism. To investigate the clinical characteristics, treatment effect, side effects and remission of hyperthyroidism in children, to analyze the predictive factors for the effect of antithyroid drug treatment, remission and recurrence after drug withdrawal, and to explore the risk factors related to the occurrence of antithyroid drug-related adverse reactions.

2. How many people will participate in the study?

About 1,000 people will participate in the study at Shengjing Hospital affiliated to China Medical University.

3. What does this study include?

1.1 Study design

single-center clinical study

1.2 Object of Study

1 . Inclusion criteria

(1) Age ≤14 years old

(2) Initial diagnosis of hyperthyroidism

2 . Exclusion criteria

(1) Hyperthyroidism had been treated with medication in other hospitals

(2) History of autoimmune hepatitis, viral hepatitis, hematological diseases, bone marrow or liver transplantation

(3) Patients with incomplete clinical data

1.3 Research Method

Children with hyperthyroidism admitted to Shengjing Hospital Affiliated to China Medical University from January 2013 to December 2022 were collected and followed up, and children with hyperthyroidism diagnosed after January 1, 2023 were continued to be included in the prospective follow-up study. The patients received MMI treatment. The initial dose of MMI was 0.2-0.8 mg/(kg▪d). This dose was subsequently reduced by 25% to 50% and adjusted to maintain euthyroidism, based on the results of serum thyroid hormone testing during follow-up.

Investigate the clinical characteristics of children suffering from hyperthyroidism, and dissect the effect of MMI treatment, remission as well as the prognostic factors of relapse subsequent to the withdrawal of MMI. Summarize the occurrence of adverse reactions following MMI treatment and delve into the factors that might influence the occurrence of adverse reactions.

1.4 For randomized study

No control group was set for the enrolled population

1.5 Drugs or procedures prohibited in the study

None

4. How long will the study last?

The study included children with hyperthyroidism who met the enrollment criteria for 10 years and collected follow-up information. You can opt out of the study at any time without forfeiting any benefits you would otherwise have received.

5. What are the risks of participating in this study?

There are no physiological risks associated with this study. However, there may be information security risks.

6. What are the benefits of participating in the study?

Patients in this study can enjoy free height and weight assessment and growth and development related consultation, and can enjoy free consultation for disease diagnosis and treatment and health problems in the later stage. Children with hyperthyroidism can enjoy green channel service in pediatric endocrine clinic.

7. Other medical options available?

If you do not participate in this study, you may continue to visit our department for systematic diagnosis and treatment.

8. Will my information be kept confidential?

We will keep your research records confidential as required by law. The relevant laws in our country provide guarantees for privacy, data and the security of authorized access. Unless required by law, your name, ID number, address, telephone number, or any other information in the research records that can directly identify you will not be disclosed outside of Shengjing Hospital Affiliated to China Medical University. For research information about you that is transmitted outside of Shengjing Hospital of China Medical University, we will use a unique number to represent you, and the coded information will be securely stored in Shengjing Hospital of China Medical University. Your identity will not be disclosed if you publish research information and data obtained from this study at scientific conferences or in scientific journals. However, your records may be reviewed to ensure that the study complies with relevant laws and regulations. The reviewers included relevant national administrative departments and the Ethics Committee of Shengjing Hospital affiliated to China Medical University.

9. About research costs?

Participants participating in the study will not incur additional costs beyond the usual treatments/tests/procedures.

10. What compensation can I get?

There was no investigator compensation for this study.

11. If a study-related injury occurs

If you damage caused by the study, the team will provide necessary medical care immediately, and in accordance with relevant laws and regulations and the medical relevant authoritative department identification, if related to the test, the pediatric endocrine genetic metabolic branch will bear the cost of treatment and the corresponding economic compensation, please contact (Shi Tang, 02496615-52311 or 18940259064)

12. Refusing to participate or withdrawing from the study

Your participation in the trial is voluntary and you may refuse to participate or withdraw from the trial in any way at any stage of the trial without discrimination or retaliation, and your medical treatment and rights will not be affected.

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After a subject drops out, no new data will be collected about them in the future. Data collected from previous studies will be retained.

13. Consulting

If you have any questions related to this study, please contact Shi Tang, landline and mobile phone (02496615-52311 or 18940259064).

If you have any questions related to your rights and interests, or if you would like to express your dissatisfaction and concerns about participating in this study, please contact the Ethics Committee Office of Shengjing Hospital Affiliated to China Medical University at 024-96615-10027.

Notification statement

"I have informed the subject and the subject's guardian of the background, purpose, procedures, risks and benefits of the retrospective and prospective study of childhood hyperthyroidism, given him/her sufficient time to read the informed consent, discuss it with others, and answer his/her questions about the study; I have told the subject to contact Shi Tang at any time when he has problems related to the research, and to contact the Ethics Committee Office of Shengjing Hospital Affiliated to China Medical University at any time when he has problems related to his own rights/interests, and provided accurate contact information; I have informed the subject that the guardian may withdraw the subject from the study at any time without any reason; I have advised that the subject will be provided with a copy of this informed consent with my and his/her signatures."

Signed by the researcher with informed consent	Phone number	Date

Informed consent statement

"My child and I have been informed of the background, purpose, procedures, risks and benefits of the retrospective and prospective study of childhood hyperthyroidism. I had plenty of time and opportunity to ask questions, and I was satisfied with the answers. I was also told who to contact when I had questions, complaints, concerns, or wanted further information. I have read this informed consent form and agree to participate in this study. I have read the informed consent form and agreed to my child's participation in the study, we have discussed the study with my child, my child has agreed to participate in the study, and I know that I can withdraw my child from the study at any time without any reason. I was told that I would get a copy of this informed consent form with my signature and that of the researcher."

Subject signature	Phone number	Date

The following methods are permitted when the subject is a minor or when the subject is unable to sign

The relationship between the legal representative and the subject_____

Signature of legal representative	Phone number	Date