Study Protocol

A Retrospective and Prospective Observational Study of Hyperthyroidism in Children

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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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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.

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

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.

Statistical analysis plan

Continuous variables were presented as median (25th–75th percentile) or mean±standard deviation and compared using the Mann–Whitney U test or independent sample t-test. Categorical variables were presented as frequency and percentage and compared using the chi-square or Fisher's exact tests. Univariate and multivariate Logistic regression analyses were used to estimate the odds ratio and 95% confidence intervals for potential risk factors for recurrence of hyperthyroidism and adverse reaction under MMI treatment. $P<0.05$ was considered statistically significant.

The problem to be solved

1. At present, most clinical studies on hyperthyroidism in children are retrospective studies with a small sample size, and this study has both retrospective and prospective studies, which is of clinical significance. Besides, more children with hyperthyroidism are admitted to the pediatric Endocrinology Department of Shengjing Hospital every year, and the sample size of this study is expected to be large.
2. To explore the clinical characteristics of children with hyperthyroidism at the first diagnosis, the effect of MMI treatment, remission and the occurrence of adverse reactions, so as to help clinicians better predict the occurrence of remission and adverse reactions, and better realize individualized treatment in the long course of treatment.

Risk and benefit

Risks: This study is non-interventional and does not pose physiological risks.

Benefits: 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.