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Research Article

Increased Incidence of Paediatric Graves' Disease in Hong Kong During the COVID-19 Pandemic

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Abstract

Background: Much clinical data suggests that during the COVID-19 pandemic, the number of autoimmune conditions including thyroid disturbances increased.

Objective: Our aim was to assess the incidence of newly diagnosed Graves' disease (GD) in children before and during the COVID-19 pandemic and its potential association with COVID-19 infection or vaccination.

Methods: A retrospective analysis was performed amongst children aged 0 to 17 years with newly diagnosed GD comparing 2017-2019 and 2020-2022 at a university hospital and regional hospital covering 3 districts in Hong Kong.

Results: Over a 6-year period, 135 children were newly diagnosed with GD. We observed an increased incidence in newly diagnosed GD during the 3 years of the pandemic compared with 3 years prior. The incidence rate of the 3 years before the pandemic was 3.0 per 100 000 person-years (95% CI, 2.2-3.8) and the incidence rate of the 3 years during the pandemic was 4.9 per 100 000 person-years (95% CI, 3.9-6.9). The incidence rate difference was 2.0 per 100 000 person-years (95% CI, 0.65-3.3; P=0.0035). The incidence rate ratio was 1.67 (95% CI, 1.16-2.41; P=0.0035). Prepandemic sex distribution showed 87% female and 13% male; giving a female-to-male ratio of 6.4:1 and during the pandemic, the sex distribution showed 78% female and 22% male; giving a female-to-male ratio of 3.6:1. The mean age of newly diagnosed GD prepandemic was 13.5 ± 2.44 years and during the pandemic mean age was 13.5 ± 2.57 years.

Conclusion: The incidence of newly diagnosed paediatric GD showed an increase during the COVID-19 pandemic compared with prepandemic in Hong Kong. In our study, there is no convincing evidence to suggest that the increase in newly diagnosed GD during the pandemic has association with COVID-19 infection or vaccination within 3 months before the diagnosis of GD.

Keywords: COVID-19; Autoimmune; Paediatric; GD Graves' disease; SARS-CoV-2

Abbreviations

COVID-19: Coronavirus Disease 2019; fT4: Free thyroxine; fT3: Free triiodothyronine; GD: GD Graves' Disease; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TSH: Thyroid Stimulating Hormone

Introduction

Graves' disease (GD) is the most common cause of autoimmune hyperthyroidism in the paediatric population [1]. Over the years, there have been reports of an increasing trend of the incidence rate in paediatric GD, but no definite reasons have been found [2]. A combination of genetic predisposition and environmental factors play a role in the disease and post viral immune dysregulation has been a proposed trigger of autoimmunity. Anti-thyroid stimulating hormone (TSH) receptor antibodies produced by the immune system binds to the TSH receptors on the thyroid follicular cells. The stimulation of the TSH receptor results in excessive thyroid hormone production. Biochemically, the TSH is supressed, and free thyroxine (fT4) and free triiodothyronine (fT3) are elevated in Graves' disease [3].

Epidemiology

GD is rare in children and is seen more during adolescent ages compared to younger ages. The incidence rate of paediatric GD or thyrotoxicosis varies around the world (Table 1). In the United Kingdom, the incidence rate was 0.1 per 100 000 person-years in younger children while it is 3 per 100 000 person-years in adolescents giving an average of 0.9 per 100 000 person-years, with a female-to-male ratio of 2.7:1 [4]. In France, the incidence rate was 4.6 per 100 000 person-years with a female-to-male ratio of 3.4:1 [5]. In Sweden, the incidence rate was 2.2 per 100 000 person-years [6]. In Denmark, the incidence rate was 1.6 per 100 000 person-years [7]. In Iceland, the incidence rate was 3.5 per 100 000 person-years with female-to-male ratio of 2.7:1 and mean age at diagnosis was 13.9 years for girls and

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Table 1: Incidence of paediatric GD or thyrotoxicosis worldwide.

Country	Incidence per 100 000 person-years	95% confidence interval per 100 000 person-years	Female-to-male ratio	Mean age		
				Female	Male	Both
United Kingdom (2010) [4]	0.9	0.8-1.1	2.7:1	Not reported		
France (2018)[5]	4.6	3.0-7.0	3.4:1	13.5	11.2	12.5
Sweden (2019)[6]	2.2	1.2-2.5	4.1:1	Not reported		13.5
Denmark (2015)[7]	1.6	1.4-1.8	4.3:1	Not reported		12.1
Iceland (2022)[8]	3.5	Not reported	2.7:1	13.9	13.6	13.8
Hong Kong (2001)[2]	5.0	2.6-8.8	9.7:1	11.5*	11.7*	11.6*

*These results were taken from raw data with permission from original Author[2].

13.6 years for boys [8]. There has not been any recorded incidence rate for paediatric GD in the United States of America; but there has been a report of a prevalence of 1 per 10,000 [9].

In Hong Kong, there was a study published in 2001 by Wong *et al.* [2] reporting the incidence of thyrotoxicosis in paediatric population up to 15 years old. Since then, there have been no other reports of the incidence rate of paediatric GD or thyrotoxicosis in Hong Kong for almost 20 years. There was a local tertiary hospital in Hong Kong that reported to have 101 newly diagnosed GD patients up to 18 years from years 2007 to 2017, but no incidence rate was reported [10]. There are also no reports of incidence in paediatric GD in other Asian countries. In adult studies, it has been reported that GD has a higher prevalence in Asian populations compared to Caucasian populations. Genetic predisposition of the human leukocyte antigen region has associated with an increase in GD in the Asian population [11].

Thyroid and COVID-19

Awareness for Coronavirus disease 2019 (COVID-19) and thyroid dysfunction has been raised globally. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19; and the role of SARS-CoV-2 infection in triggering autoimmunity in new onset GD has been observed [12,13]. Several studies have reported thyroid autoimmunity during the acute phase and after COVID-19 infection. There have also been reports of autoimmune thyroid disturbances after the application of various COVID-19 vaccines [14].

There has been proposed pathophysiology of COVID-19 induced thyroid disturbances according to voluminous recent publications. One theory is that SARS-CoV-2 may cause thyroid dysfunction through direct cell damage by entering through angiotensin-converting 2 (ACE-2) receptors or other reasons of indirect mechanisms which include autoimmunity triggering or accelerating effects [15-17].

A large adult study was performed in Hong Kong during the COVID-19 pandemic and found that COVID-19 infection increases the risk for GD but COVID-19 vaccination did not increase the risk for GD which is consistent with previous studies [18]. There has been literature reporting increased incidence of GD in paediatric patients during COVID-19 pandemic associated with an increased in severity of symptoms in youths needing increased used of betablockers. The severity is likely due to the stress of the COVID-19 pandemic and delays in presentation [19]. Children tend to be more protected from the complications of acute disease of COVID-19 infection; however, there may be some long-term consequences in which there are continued observations. All in all, data on COVID-19 in children and the thyroid gland is sparse and there is much knowledge that needs to be gained [14].

Objective

The objective of this study is to determine the impact of the pandemic on the incidence of newly diagnosed GD in children and whether COVID-19 infection or vaccination has any association towards this.

Materials and Methods

Study Design and Setting

Data was collected retrospectively via Hospital Authority's Clinical Data Analysis and Reporting System (CDARS) with standardised data from two hospitals including Prince of Wales Hospital and Alice Ho Miu Ling Nethersole Hospital of New Territories East Cluster in Hong Kong. Newly diagnosed paediatric GD from January 1, 2017 until December 31, 2022 who were younger than 18 years old at diagnosis were studied. The CDARS searched for keywords including "Graves' disease", "thyrotoxicosis" and "hyperthyroidism" during this period. Patient demographic data and clinical information were collected from medical records. COVID-19 infection and vaccination status were taken from the COVID-19 indicator from the Department of Health of Hong Kong. Census data was obtained from the Statistics Department of the Hong Kong Government. The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

Inclusion and Exclusion Criteria

All children in our catchment area aged 0-17 years with newly diagnosed GD between January 1, 2017 and December 31, 2022 in the two public hospitals were included. Exclusion criteria included subjects 18 years and older at diagnosis, multinodular goitre, neonatal thyrotoxicosis and Hashimoto's thyroiditis.

Measured Parameters

Demographic data collected included patient's sex, age at diagnosis and date of diagnosis. Clinical features of GD were recorded, and biochemical data collected included fT4, fT3 and TSH levels. Dates of COVID-19 infection and vaccination were recorded for those patients who had their GD diagnosis during the pandemic.

The diagnosis of GD was made by the presence of clinical features of hyperthyroidism, diffuse, non-nodular and non-tender goitre, and elevated fT4 or fT3 with suppressed TSH levels [20]. For patients diagnosed with GD during the COVID-19 pandemic, we defined GD associated with COVID-19 infection as GD diagnosed within 3 months after COVID-19 infection [21-23]; and GD associated with COVID-19 vaccination as GD diagnosed within 3 months after COVID-19 vaccination [24].

Statistical Analysis

Data was extracted and descriptive statistics were reported in incidence rate per 100 000 person-years, mean, standard deviation, difference and ratio. The confidence interval of the difference between two rates was measured using Test-based Method and the P-value is obtained using the Chi^2-statistic. The Exact Poisson Method was used for the confidence interval of the incidence rate ratio. A P-value of <0.05 was considered statistically significant.

Statistical calculations were made by IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp. Released 2021. Armonk, NY: IBM Corp), and R software (v4.2.1) and MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

The primary search identified 142 patients using CDARS. Patients excluded are as follows: 1 patient with multinodular goitre, 1 patient with neonatal thyrotoxicosis. Both patients were diagnosed prepandemic. There were 3 patients prepandemic and 2 patients during the pandemic with Hashimoto's thyroiditis. From year 2017 to 2022, 135 newly diagnosed GD patient data were analysed.

During the 6-year period from 2017 until 2022, the number of newly diagnosed GD in Chinese paediatric patients increased as time went by. Prepandemic: 2017 (n=24), 2018 (n=12), 2019 (n=16) and during the COVID-19 pandemic: 2020 (n=18), 2021 (n=31), 2022 (n=34) as shown in Figure 1.

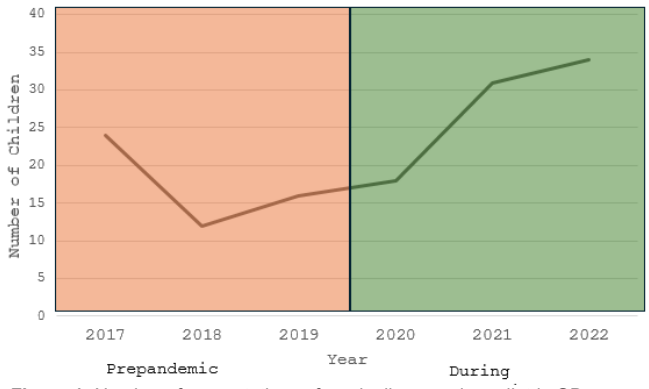

Figure 1: Number of presentations of newly diagnosed paediatric GD per year.

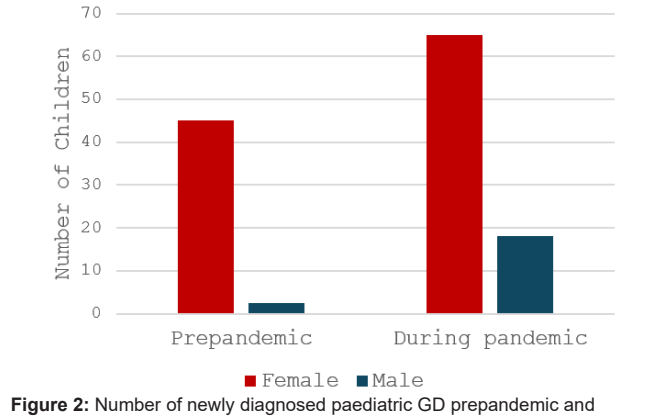

Figure 2: Number of newly diagnosed paediatric GD prepandemic and during pandemic for females and males.

The incidence rate prepandemic was 3.0 per 100 000 person-years (95% CI, 2.2-3.8) compared to during the COVID-19 pandemic of 4.9 per 100 000 person-years (95% CI, 3.9-6.9). The incidence rate difference was 2.0 per 100 000 person-years (95% CI, 0.65-3.3; P=0.0035). The incidence rate ratio was 1.67 (95% CI, 1.16-2.41; P=0.0035).

Prepandemic sex distribution showed female (87%, n=45) predominance compared to male (13%, n=7), female-to-male ratio was 6.4:1. During the COVID-19 pandemic the sex distribution also showed female predominance (78%, n=65) when compared to male (22%, n=18) female-to-male ratio was 3.6:1 as shown in Figure 2. When comparing the prepandemic and during pandemic female-to-male ratio, it is not statistically significant (P=0.192).

For age at diagnosis, prepandemic mean age was 13.5 ± 2.44 years and during the COVID-19 pandemic, mean age was 13.5 ± 2.57 years. The association between age at diagnosis pre and during the COVID-19 pandemic was not significant.

During the COVID-19 pandemic period, there were 6 out of 83 (7%) patients that had COVID-19 infection within 3 months prior the diagnosis of GD; 5 of those were female and 1 was male. There were 13 (16%) patients had COVID-19 vaccinations within 3 months prior the diagnosis of GD and of those; 9 were female and 4 were male. For the vaccinations, 7 (54%) had Fosun-BioNTech and 6 (46%) had Sinovac vaccination.

Discussion

This retrospective observational study found that the incidence of newly diagnosed paediatric GD increased during the COVID-19 pandemic for Chinese children in Hong Kong. This is in line with other reports in both the paediatric population in the United States [19] and the adult population in Hong Kong [18] and Spain [25]. It is difficult to compare our results with other countries of geographical proximity in Asia as there are no other Asian countries that report the incidence of paediatric GD.

GD is well known to be a female predominant disease [26,27]. Hong Kong has always reported a higher number for female predominance compared to worldwide with female-to-male ratio between 8.2:1 [1] and 9.7:1 [2]. In our study, the finding of female predominance existed both before and during the pandemic. However, there was a decrease in female-to-male ratio from 6.4:1 prepandemic to 3.6:1 during the COVID-19 pandemic although the difference was not shown to be statistically significant. There was only 1 male that had COVID-19 infection within 3 months before his GD diagnosis. Four out of 13 patients were male who had COVID-19 vaccination within 3 months before their GD diagnosis. These numbers are too small to show significant association with the change in the female-to-male ratio.

Despite the increase in numbers of newly diagnosed GD during the COVID-19 pandemic in our study, the mean age at diagnosis before and during the pandemic remained the same at 13.5 years which is in fact, higher than the mean age reported for paediatric GD of similar ethnicity in Nanjing, China (8.9 ± 2.9 years) [27]; but similar to other reported ages worldwide (12.1-13.8 years) [5-8].

Concerning the possible association between SAR-CoV-2 infection and GD; it is proposed that the mRNA that encodes the

ACE-2 receptor of the follicular cells in the thyroid. The ACE-2 receptor then allows the SARS-COV-2 to enter host which leads to viral replication and transmission [15]. One important mechanism for initiating an autoimmune reaction is molecular mimicry in which a foreign derived antigen which can be SARS-CoV-2; resulting in activation of autoreactive T and B cells. Other things that affect molecular mimicry are genetics, microbiota and environmental chemicals [17]. Back to the finding of our study, the number of patients who had COVID-19 infection within 3 months before their GD diagnosis was small (6 out of 83; 7%), therefore we could not find a direct association between COVID-19 infection and the increased incidence of paediatric GD during the pandemic in our locality.

Regarding whether the COVID-19 vaccine is potentially an association of autoimmunity triggering GD, there is no definite evidence from literature, but awareness is raised for healthcare professionals for the possibility [28]. There have already been other studies showing Pfizer-BioNTech vaccine is safe in children regarding thyroid autoimmunity [14]. Also, a large population-based study was performed in adults to show that there is no evidence of vaccine-related increased incidence of thyroid dysfunction with BNT162b2 and CoronaVac [29]. The vaccines used in our locality was Fosun-bioNTech and Sinovac. In our study, 16% of patients had a COVID-19 vaccine within 3 months before their diagnosis of GD which is not a substantial number and difficult to regard as an association with GD.

Limitations

There are several limitations of this study. Firstly, despite our study showing that there is increased incidence of paediatric GD during the COVID-19 pandemic, there are no reports on the incidence of paediatric GD in Hong Kong after 1998 to 2017. There is a knowledge gap that we do not know the trend of incidence of paediatric GD for almost 2 decades prior 2017. Furthermore, there is difficulty in directly comparing the finding of our study with previous local data reported in 2001 by Wong *et al.* [2] who looked at thyrotoxicosis and not just GD. Also, Wong *et al* [2] included patients who were less than 16 years of age but the age range of patients in our study was less than 18 years old.

Secondly, this study included paediatric patients in our catchment area with GD who presented to our two public hospitals. There is a possibility that our incidence is underestimated as there maybe children that presented and were managed in the private sector; especially during the COVID-19 pandemic when people were reluctant to come to public hospitals.

Thirdly, the number of patients with COVID-19 infection may be underestimated. During the start of the COVID-19 pandemic, all paediatric patients who had COVID-19 infections were hospitalised due to government policy. However, those who did not present themselves to medical professionals could not be recorded. In addition, mandatory hospitalisation of COVID-19 stopped in late 2021 which meant any COVID-19 infections were down to self-reporting to the Hong Kong government. This could mean that there may be underreporting of COVID-19 infections in the year 2022.

Finally, our study is a retrospective observational study in which we are unable to obtain complete information for all the important confounding or risk factors related to GD before and during the COVID-19 pandemic, and some data is bound to missing. Therefore, it is difficult to further evaluate the relationship between the increased incidence of paediatric GD and other possible risk factors.

Conclusion

This study shows an increase in the incidence rate of paediatric Graves' disease in Hong Kong during the COVID-19 pandemic. There was a decreasing trend of female-to-male ratio during the pandemic although the change is statistically insignificant. The mean age of paediatric Graves' disease at diagnosis remained the same over the 6-year period. There is no convincing evidence to show that COVID-19 infection or COVID-19 vaccine is associated with this higher incidence of Graves' disease. Continued further research is needed to identify any genetic or environmental factors associated with the epidemiology of Graves' disease in children.

Ethical Statement

The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee.

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