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Original Article

Portrayal of Thyroid Abnormalities and Their Management in a Local Cohort of Children and Adolescents with Down Syndrome: An Update

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Abstract ***Objective:*** Evaluation of the prevalence of different thyroid disorders and co-morbidities in children and adolescents with Down syndrome (DS). ***Methodology:*** Retrospective review of medical records from a tertiary referral centre in Hong Kong from 2002 to 2017. Prevalence of different thyroid disorders and associations with co-morbidities were calculated. ***Results:*** Among the 157 patients enrolled in analysis, impaired thyroid function was found in 58 (36.9%) patients. The most common form of thyroid-related disorder was subclinical hypothyroidism. Of note, 4.5% of them had oscillating thyroid diseases. Anti-thyroid antibody testing was done in 19% of the patients. Haematological malignancies were significantly associated with development of any thyroid diseases (p=0.026). Fifty percent of DS patients were shown to be affected by thyroid abnormalities by 22.9 years. ***Conclusion:*** Thyroid abnormalities are very common among children with DS. Anti-thyroid antibody testing is indicated in older children to delineate the risk of development or persistence of thyroid diseases. Consensus is needed to standardise the time points of thyroid function evaluation especially during early stages of life.

Key words *Down syndrome; Hypothyroidism; Hypothyroidism; Thyroid diorders*

Background

Down syndrome (DS) is one of the commonest survivable autosomal aneuploidy,[1] occurring in one of 600 to 800 live births. Thyroid dysfunction is a well-recognised endocrinopathy experienced by patients with DS, with a lifetime prevalence ranging from 13 to 63%.[2]

Being a treatable cause of mental retardation, timely detection and treatment of hypothyroidism are pivotal to optimise the cognitive capacities and improve the quality of life in this already impaired population, especially when the onset of hypothyroidism may be associated with symptoms and clinical findings that are subtle (e.g. macroglossia, developmental delay, feeding difficulties and constipation) and easily attributed to the underlying disorder.

In the last retrospective epidemiological study on DS in Hong Kong published in year 2006, covering 1986 to 2001, it has revealed thyroid dysfunctions were very prevalent (28.8%) in DS population in our locality. Among which, the majority was subclinical hypothyroidism (22.5%).[3]

There have been disparities in opinions with regard to the association between congenital hypothyroidism and DS. Although Fort et al found congenital hypothyroidism to be more common among infants with DS than in the general population, some other references challenged this observation. There have also been debates on optimal timepoints for screening thyroid function in DS children especially during the first year of life. The American Academy of Pediatrics (AAP) recommends that thyroid functions in DS children should be monitored at birth, at 6 and 12 months of age then annually.[2,4-6] However, recent studies adding extra timepoints between birth and six

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months of life revealed significant cases of hypothyroidism requiring thyroxine supplementation.

The correlation of acquired thyroid diseases and DS in older children, mostly autoimmune in origin, is otherwise better established and accepted over the years.[7] Furthermore, thyroxine therapy in DS children with subclinical hypothyroidism, or termed isolated hyperthyrotropinemia or compensated hypothyroidism has remained the object of debate. Some authors concluded that thyroxine replacement was seldom required in subclinical hypothyroidism in children with DS, as in those of the general population. A recent meta-analysis in adult non-pregnant subclinical hypothyroid patients concluded thyroxine replacement did not improve the general quality of life or thyroid-related symptoms.[8] On the contrary, other authors suggested that therapy should be forthcoming, even in mild cases, because such treatment prevents the development of more severe hypothyroidism.

More than one decade after our last local study, it is therefore about time to revisit the prevalence of the thyroid status and pattern of clinical management in this needed population in our locality and to compare with the disputable observations in other countries.

Objectives

The primary objective of this study was to determine the prevalence of thyroid disorders among children and adolescents with DS in our locality; while the secondary objectives were to investigate the co-existence of congenital anomalies and/or co-morbidities, the incidence of autoantibodies, as well as their relationship with thyroid dysfunctions. Clinical management on the thyroid disorders, particularly the threshold of commencing thyroxine replacement in subclinical hypothyroidism was also evaluated.

Methodology

Study Design and Subjects

This was a retrospective cohort study of all children and adolescents with DS (ICD-10 code 758.0) who were admitted to the paediatric units or attended the specialist out-patient clinics of Princess Margaret Hospital from 1st January 2002 to 31st December 2017. Subjects were excluded when their hard and electronic data could not be retrieved. This study was approved by the Institutional Review Board or Research Ethics Committee of Kowloon West Cluster.

Data Collection

The hospital records were retrieved using the Clinical Data Analysis and Reporting System (CDARS) with the following data reviewed: demographics, growth parameters, karyotypes, co-existence of congenital anomalies and/or co-morbidities, thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid antibodies (anti-thyroglobulin and anti-thyroid peroxidase levels) at the time of diagnosis of a thyroid disorder or at their latest presentation if their thyroid status has remained normal, investigations including thyroid scan and ultrasound scan of the thyroid gland. Age at the beginning of therapy, thyroxine and anti-thyroid medication dose at initiation and last visit were also recorded. The record tracing would be limited to the period when the patients have been managed by paediatricians if they have already reached the adult age range and followed up by the adult medical counterpart.

Thyroid disease was characterised as congenital hypothyroidism, acquired hypothyroidism, subclinical hypothyroidism and hyperthyroidism as per the criteria defined by the American Thyroid Association (ATA),[9] or as stated in the medical record, with the additional taxonomies of unspecified hypothyroidism, oscillating thyroid disease, transient hypothyroidism and transient hyperthyroidism for more prudent categorisations (Table 1). Cases of subclinical hypothyroidism were further separated into those TSH 5-10 mIU/L and those with TSH greater than 10 mIU/L. If the diagnostic data was not available, classification would be based on the available abnormal thyroid functions within six months before starting treatment.

Statistical Analysis

Data were presented in count with percentage, mean with standard deviation (SD) or median with interquartile range (IQR). Prevalence of thyroid disease with 95% confidence interval (CI) was calculated. Chi-squared tests or Fisher's exact tests were used to compare categorical variables. Continuous variables were compared by Kruskual Wallis test among different thyroid disease status. Proportion of patients affected by thyroid disease with age was illustrated with Kaplan-Meier curve. All statistical data was analysed by Statistical Package for Social Sciences (SPSS) software (version 22). P-value of less than 0.05 was considered as statistical significant.

Results

A total of 157 patients were enrolled in the study after excluding 11 patients with data not retrievable. There were 99 males (63.1%) and 58 females (36.9%). The majority was Chinese (97.4%), with one Japanese, one Korean and two Pakistani. The most common co-morbidity in the cohort was congenital cardiac disease (43.3%). Among the cohort, 99 patients had normal thyroid function throughout the course of paediatric follow-ups. The thyroid disease prevalence was 36.9% (95% CI 29.79% to 44.72%). The comparison of karyotyping information, congenital anomalies and co-morbidities in patients with and without thyroid diseases were described in Table 2. There was no association found between developing any thyroid diseases and gender, ethnicity, karyotype or different co-morbidities, except leukemia or myeloproliferative disorders (p=0.026). There were six patients (3.8%) with leukemia or myeloproliferative disorders, five of whom had developed thyroid diseases.

Table 3 shows the details of different thyroid diseases. Among 58 patients with a thyroid-related diagnosis, three (1.9%) had congenital hypothyroidism, six (3.8%) had acquired hypothyroidism, 18 (11.5%) had subclinical hypothyroidism, three (1.9%) had unspecified hypothyroidism, seven (4.5%) had hyperthyroidism, seven (4.5%) had oscillating thyroid disease, 14 (8.9%) had transient hypo/hyperthyroidism. The TSH and FT4 levels were statistically significantly different among the thyroid disease groups (p<0.001 and p=0.007, respectively). The anti-thyroid antibody positivity was statistically significant between the disease groups (p=0.007), but only 30 (19%) patients were tested with 12 of them having one or both antibodies positive. For those with normal thyroid function, only one was tested for anti-thyroid antibodies which were negative.

Among seven patients with congenital or subclinical hypothyroidism diagnosed below the age of one, five were diagnosed between newborn and six months of age, i.e. between the first and second time points for thyroid function evaluation in DS children as per AAP recommendation.[4] For the five patients diagnosed between newborn and six months of age, three of them were congenital hypothyroidism and two were subclinical hypothyroidism. All of the five patients were started on thyroxine supplement.

Seven patients had pure hyperthyroidism with the mean age of diagnosis at 13.01 years. For the seven patients with oscillating thyroid disease, most of them developed hypothyroidism first, then gradually moved to have hyperthyroidism. Their thyroid pertubations all developed in their adolescence. It did not see a gender predominance. Antibody positivity was remarkably higher in patients with hyperthyroidism (four out of five tested) and oscillating thyroid disease (six out of seven tested).

Thyroid scan was done in 10 patients, three were congenital hypothyroidism, two acquired hypothyroidism, three subclinical hypothyroidism and two transient

Table 1 Diagnostic criteria for different types of thyroid diseases

Thyroid disease	Diagnostic criteria*
Congenital hypothyroidism	High TSH with low FT4 diagnosed within the first month of life, or as stated in the medical record
Acquired hypothyroidism	High TSH with low FT4 after first month of life, or as stated in the medical record
Subclinical hypothyroidism	High TSH with normal FT4 at diagnosis, or as stated in the medical record
Unspecified hypothyroidism	High TSH with low FT4 with unspecified time point at diagnosis, or when FT4 level was not available
Hyperthyroidism	Low TSH with high FT4 at diagnosis, or as stated in the medical record
Oscillating conditions	The change of hypothyroidism to hyperthyroidism, or in the opposite sequence, during the study period
Transient hypothyroidism	Transient high TSH with low or normal FT4, which later reverted to normal, which may or may not require replacement therapy
Transient hyperthyroidism	Transient low TSH and/or elevated FT4, which later reverted to normal, which may or may not require anti-thyroid therapy

Abbreviations: TSH, thyroid stimulating hormone; FT4, free thyroxine

*High and low were assessed as per the reference ranges of the individual laboratories

Table 2 Demographics and co-morbid diagnoses in the cohort*

		Thyroid related diseases		
	Total (n=157)	**No (n=99)**	**Yes (n=58)**	***p* value†**
Age at diagnosis (year) - median [IQR]	–	–	8.2 [1.5 - 16.2]	–
Gender				0.884
Male	99 (63.1)	62 (62.6)	37 (63.8)	
Female	58 (36.9)	37 (37.4)	21 (36.2)	
Ethnicity‡				0.130
Chinese	150 (97.4)	98 (99.0)	52 (94.5)	
Non-Chinese	4 (2.6)	1 (1.0)	3 (5.5)	
Karyotype‡				1.000
Trisomy 21	64 (94.1)	31 (93.9)	32 (91.4)	
Mosaicism	3 (4.4)	2 (6.1)	1 (2.9)	
Robertsonian translocation	1 (1.5)	0	1 (2.9)	
Congenital cardiac disease				0.430
No	89 (56.7)	60 (60.6)	29 (50)	
Yes without operation	45 (28.7)	26 (26.3)	19 (32.8)	
Yes with operation	23 (14.6)	13 (13.1)	10 (17.2)	
Visual impairment§	50 (31.8)	34 (34.3)	16 (27.6)	0.380
Hearing impairment	36 (22.9)	19 (19.2)	17 (29.3)	0.145
Sleep apnoea	15 (9.6)	9 (9.1)	6 (10.3)	0.796
Gastrointestinal disease				0.728
No	129 (82.2)	81 (81.8)	48 (82.8)	
Duodenal atresia / Hirschsprung disease / Imperforate anus	14 (8.9)	10 (10.1)	4 (6.9)	
Others§	14 (8.9)	8 (8.1)	6 (10.3)	
Leukaemia / myeloproliferative disorders	6 (3.8)	1 (1.0)	5 (8.6)	0.026
Orthopaedics				0.622
No	131 (83.4)	84 (84.8)	47 (81.0)	
C1/2 subluxation	14 (8.9)	9 (9.1)	5 (8.6)	
Others§	12 (7.6)	6 (6.1)	6 (10.3)	
Undescended testes (for male only)	9 (9.1)	5 (8.1)	4 (10.8)	0.724
Diabetes	1 (0.6)	0	1 (1.7)	0.369
Obesity	14 (8.9)	8 (8.1)	6 (10.3)	0.631
Psychological disturbance	6 (3.8)	2 (2.0)	4 (6.9)	0.194
Seizures	5 (3.2)	3 (3.0)	2 (3.4)	1.000
Renal abnormalities§	12 (7.6)	5 (5.1)	7 (12.1)	0.128

*Values are presented as count (%), except where noted

†Pearson's chi-square test or Fisher's exact test

‡With missing data

§Visual impairment include astigmatism, strabismus, cataract, myopia and hypermetropia; other gastrointestinal diseases include gastroesophageal reflux, irritable bowel syndrome, constipation, inguinal hernia, umbilical hernia, gallstone; other orthopaedics include hallux valgus, flat foot; renal abnormalities include renal parenchymal disease, nephrocalcinosis, dilated renal collecting system

hypothyroidism. Thyroxine had been started in eight out of these 10 patients. Ultrasound thyroid was only performed in three patients.

Thyroxine replacement was required in 22 patients with the mean age of thyroxine commencement at 6.98±7.68 years (range: 0.01 to 22.62 years), dependent on the indications of treatment. The mean TSH of thyroxine commencement was 64.0±119.5 mIU/L (range: 2.6 to 500 mIU/L). Seven (31.8%) of them were replaced with thyroxine when their TSH was less than 10 mIU/L. Thirteen patients were treated with anti-thyroid drugs (ATD). All of the ATDs were carbimazole. The mean age of carbimazole commencement was 16.2±5.49 years (range: 2.92 to 22.93 years), which is much older than that for thyroxine.

Discussion

This study confirmed the previously reported high prevalence of thyroid problems in DS patients in the defined study period. In line with the findings by Mak et al, subclinical hypothyroidism was the most prevalent thyroid abnormality in DS children, the mean age of diagnosis of hyperthyroidism was the oldest among all categories of thyroid abnormalities.[3]

We acknowledged and addressed the findings in the previous local cohort study. We intended that the features distinguishing the current study from the previous publication would be (a) discussion of the inadequacy of AAP recommendations on thyroid screening in DS children, (b) occurrence and discussion of oscillating thyroid disease, (c) address on the variability of TSH thresholds at the commencement of thyroxine for treatment of hypothyroidism.

The incidence of congenital hypothyroidism (CH), which comprised of three DS patients (1.9%) in the cohort over the study period of 15 years was the same in our local population over another 15 years prior to our study period.[3] CH was therefore not the most accountable aetiology of thyroid abnormalities in DS children and adolescents. It could be explained by the observation that congenital hypothyroidism diagnosed at newborn, and after newborn and before six months is of non-immune aetiology, whereas the prevalence of thyroid problems in DS is associated with autoimmunity.[10] A previous study showed no cases of autoimmune positivity before the age of eight.[11] In our cohort, the mean age with positive antibodies was 13.17 years. None of the cases diagnosed during infancy was

Table 3 Prevalence of different thyroid diseases and the presence of anti-thyroid antibodies*

Thyroid disease	Total	Male	Age at diagnosis (years)	TSH (mIU/L)	FT4 (pmol/L)	Anti-thyroid antibody Tested	
						Total	Positive
Congenital hypothyroidism	3 (1.9)	2 (66.7)	0.07± 0.04	37.42±18.36	14.70±5.66	2 (66.7)	0
Acquired hypothyroidism	6 (3.8)	5 (83.3)	9.23±8.47	90.25±200.79	9.55±3.31	6 (100)	1 (16.7)
Subclinical hypothyroidism	18 (11.5)	11 (61.1)	6.14±5.92	7.64±3.34	12.89±3.23	7 (38.9)	1 (14.3)
TSH 5 - 10 mIU/L	*13 (8.3)*	*6 (46.2)*	*6.51±5.84*	*5.83±1.32*	*13.28±3.45*	*3 (23.1)*	*1 (33.3)*
TSH > 10 mIU/L	*5 (3.2)*	*5 (100)*	*5.17±6.72*	*12.32±2.05*	*11.96±2.7*	*4 (80)*	*0*
Unspecified hypothyroidism†	3 (1.9)	1 (33.3)	2.99	8.20	–	0	–
Hyperthyroidism	7 (4.5)	2 (28.6)	13.01±5.73	0.05±0.06	39.15±17.75	5 (71.4)	4 (80)
Oscillating conditions	7 (4.5)	4 (57.1)	18.33±4.82	30.28±71.42	26.87±21.49	7 (100)	6 (85.7)
Transient hypothyroidism	13 (8.3)	11 (84.6)	7.91±8.17	7.74±3.7	13.44±2.64	2 (15.4)	0
Transient hyperthyroidism	1 (0.6)	1 (100)	19.09	1.35	26.60	0	–
Normal thyroid function	99 (63.1)	62 (62.6)	–	2.06±0.89	12.53±2.82	1 (1)	0
p value‡	–	0.214	0.003	<0.001	0.007	–	0.007

Abbreviations: TSH, thyroid stimulating hormone; FT4, free thyroxine

*Values are presented as count (%) or mean ± SD

†With missing data

‡Comparison among disease groups using Fisher's exact test or Kruskual Wallis test

associated with positive antibodies.

With the advent of medical technology, it was realised that the biochemical evidence of hypothyroidism often supersedes clinical symptoms. And when worst comes to worst, DS features and hypothyroidism overlap and both contribute to developmental delay. In our cohort, five patients were diagnosed before the six-month thyroid function screening recommended by the AAP.[4] Their recommendations, largely based on expert opinions, had produced a hot debate among the endocrinologists on the diagnosis and treatment decisions. Although we have universal newborn screening for thyroid function, the screening might still have the problem of false negativity.[12] A cohort study done in a university-based birthing hospital rescreened a total 122 neonates with DS before four months of age who had normal newborn thyroid screening and found 17.4% with hypothyroidism requiring thyroxine replacement.[6] Adding more time points for screening before six months of age may detect early cases of hypothyroidism who passed their newborn screen and might improve their developmental trajectory by timely intervention, when there is no doubt that congenital hypothyroidism is the most treatable cause of mental retardation. Delaying thyroxine replacement after three months poses higher risk of mental retardation.[13] The additional screening, with the test itself not burdening much extra cost, could be done without additional paediatrician visits.

Seven patients in our cohort demonstrated oscillating thyroid disease, i.e. development of hypothyroidism then progressed to hyperthyroidism, or in the converse. For patients developing hyperthyrodisim first, two of them progressed to hypothyroidism and then developed hyperthyroidism again. Six out of seven had positive anti-thyroid antibodies. This is a very peculiar feature in DS, with Graves' disease (GD) often preceded by Hashimoto thyroiditis (HT).[14] While there exists a continuum between HT and GD within the spectrum of autoimmune thyroid disorders (AITDs),[15] DS patients are at higher risk of progression from HT to GD, irrespective of other concomitant risk factors.[14,16] In our latest local study of juvenile GD in Hong Kong, the female to male ratio in our local study was up to 9.7.[17] There were five females and two males diagnosed hyperthyroidism in our cohort, in contrast to three females and four males in the group of oscillating thyroid disease. The loss of gender predominance is in concordance with the literature findings.[16]

Among those medicated with thyroxine, 31.8% of them were started on replacement when their TSH was less than 10 mIU/L. The benefit of thyroxine replacement in subclinical hypothyroidism is debatable. The general perception is biased towards treatment which is beneficial and doing little harm. Yet newer studies have proven that early thyroxine treatment in DS children with hyperthyrotropinemia (TSH ≥5 mIU/L) did not improve mental or motor developmental achievement in their later life despite there was measurable positive effect on growth.[18] A large retrospective study also showed a 73.6% normalisation rate in five years follow-up if TSH was between 5 and 10 mIU/L in a cohort of over 120,000 paediatric patients.[19]

Meanwhile, some authors opined DS patients have a non-pathological shift in the normal range of TSH and may lead to overdiagnosis of subclinical hypothyroidism.[20] Another observational study also revealed that DS newborns had a lower total T4 concentration in combination with a higher TSH concentration compared with non-DS newborns.[21] Hyperthyrotropinemia is an inherent attribute of chromosomopathy in DS that alters the hypothalamic-pituitary-thyroid axis.[22]

On the other hand, Aversa et al revealed higher risk of deterioration of thyroid status in Hashimoto thyroiditis related subclinical hypothyroidism (SH) compared with idiopathic SH.[21,23] This emphasizes the importance of antibody testing in SH patients. Only 19% of our cohort had the antibody screening done.

The authors believed the normalisation of thyroid status in the group of transient hypothyroidism may be associated with negative antibody if screening had been performed. In our cohort, only two patients (15.4%) among the group of transient hypothyroidism were screened for anti-thyroid antibodies, with none of them being positive. The mean age of normalisation of thyroid function in the transient groups was 12.4 years. Nonetheless, there have been diversifying opinions with regard to the time course and natural history of hypothyroidism.[5,24]

Owing to the high lifetime prevalence of thyroid diseases in DS patients (Figure 1) and the association between autoimmunity and development of persistent thyroid diseases, anti-thyroid antibody screening could shed light on selecting DS patients who are more probable to develop overt hypothyroidism and hence closer follow up.

Concerning the co-morbidities of DS, previous studies concluded that there were no association between congenital heart diseases and thyroid abnormalities.[25] However, congenital hypothyroidism is noted to occur more commonly in DS patients with congenital gastrointestinal anomalies,[26] though this was not observed in our cohort. The only significant association we found was between haematological malignancies and thyroid

diseases (p=0.026). Although not widely reported, there were postulations between the two given the immunological abnormalities in DS patients.

There are a few limitations in this study. Firstly, the sample size is small from our single centre, with many missing data when the electronic and hard copies of the case notes could not be retrieved. The registrants in the cohort are not considered to represent the full population of DS children. There is heterogenous distribution of ethnicities in this metropolitan city. Our cluster might be skewed to be Chinese in majority but not the others. Secondly, small number of patients were screened for thyroid antibodies, especially those with transient hypothyroidism and registrants not labelled having a thyroid-related disorder. Thirdly, the definition of subclinical or overt hypothyroidism (congenital, acquired or unspecified) in some cases might be ambiguous owing to early commencement of thyroxine when the hormonal manifestation had not yet been full-blown. This would affect our data analysis and comparison. Finally, the hormonal and antibody analyses came from different laboratories over the 15-year study period when the assay methodologies might have been updated. The same analyte would be reported by different reference ranges that might pose difficulties on our interpretations.

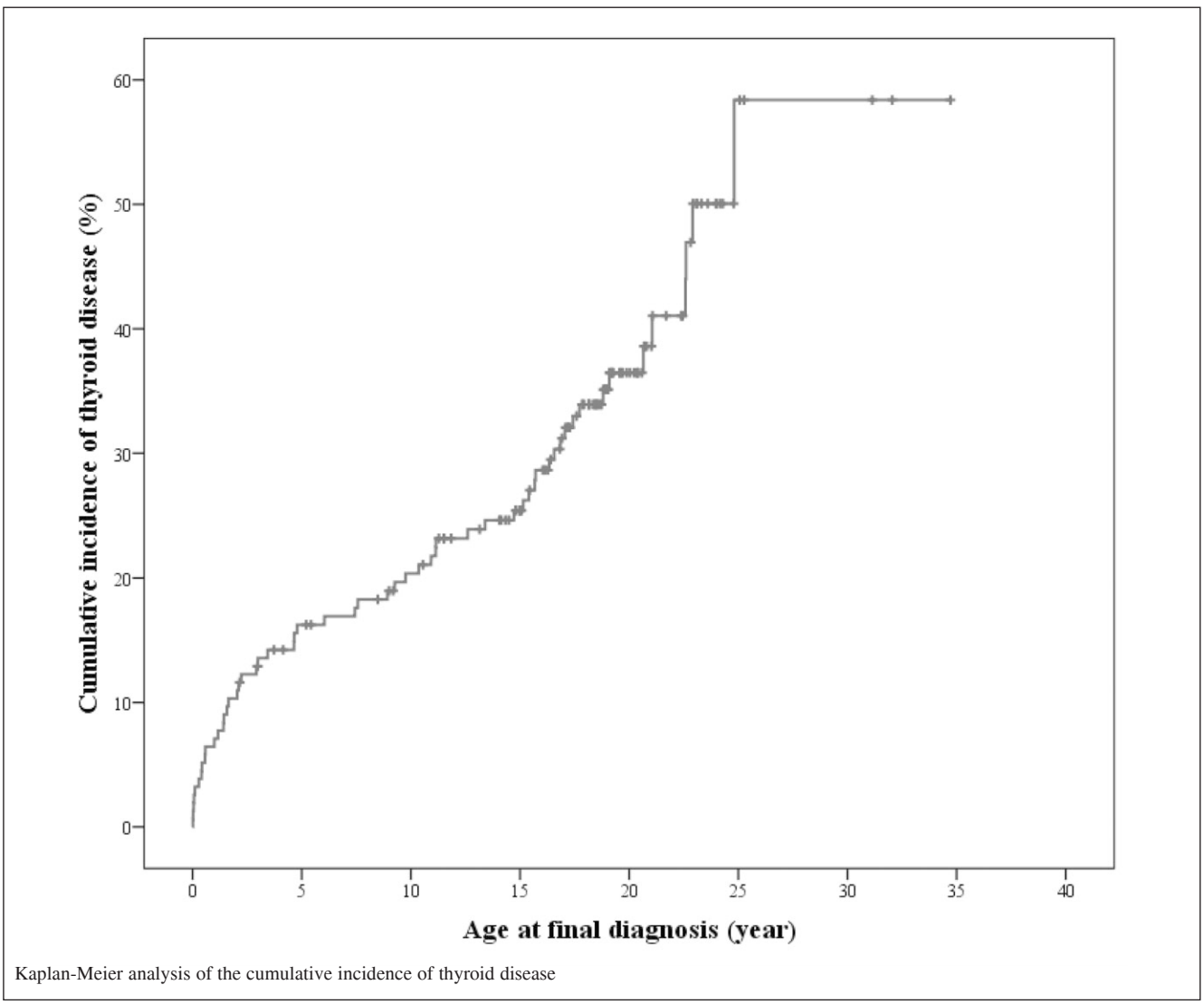

Figure 1 Demonstrated the Kaplan-Meier cumulative lifetime prevalence curve, illustrating the development of thyroid diseases with age. There were 25% of DS patients with a diagnosis of thyroid dysfunction at 14.7 years and 50% at the age 22.9 (95% CI 21 to 24.9 years). Therefore one in two DS patients would be affected by thyroid disease when they reach adulthood.

Conclusion

Thyroid abnormalities are common in children and adolescents with DS. More frequent thyroid function evaluations on top of the AAP recommendations could enhance earlier detection and intervention. However, despite the treatment is usually safe, there is debate on the TSH threshold of thyroxine contemplation in SH which might not produce the expected favourable outcomes as previously reported. Anti-thyroid antibody testing allows closer follow up and timely treatment especially when they have SH. Future studies may consider developing age-specific reference ranges for TSH and FT4 specific to DS patients. Consensus is needed to establish the working definition of euthyroidism and hypothyroidism, standardise the screening and management of thyroid abnormalities in children and adolescents with DS.

Declaration

I declare that this dissertation represents my own work and this paper has not been published before. There is no conflict of interest concerning this study.

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