

MEDICAL GENETICS

Thyroid dysfunction in a cohort of South African children with Down syndrome

S Moosa,¹ MB BCh, DCH (SA), MMed, FCMG (SA); D G Segal,² MB BCh, FAAP (USA); A L Christianson,¹ MB ChB, FRCP (Edin); N E Gregersen,¹ MB BCh, MSc (Med), DCH (SA), FCPaed (SA), Cert Med Genet

¹ Division of Human Genetics, National Health Laboratory Service and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

² Department of Paediatrics, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author: S Moosa (shahidamoosa@gmail.com)

Background. While international studies show thyroid dysfunction occurs more commonly in individuals with Down syndrome (DS) than in the general population, there is a paucity of available data from sub-Saharan Africa.

Objectives. To document the range of thyroid function in a cohort of South African children with DS, and to assess referral and treatment practices when thyroid dysfunction was present.

Methods. A retrospective file-based study of 391 children with DS seen at the genetic clinics at three Johannesburg hospitals from 2003 to 2008. Thyroid function test (TFT) results (thyroid-stimulating hormone and free thyroxine) and demographic details were collected for each child. Endocrine clinic files from two of the hospitals were reviewed for additional referral and treatment information.

Results. The majority (83.6%) of children had at least one TFT, in most cases performed between the ages of 2 and 12 months. The most common form of thyroid dysfunction was subclinical hypothyroidism (SCH) (28.7%). Up to one-third of the patients, including several neonates with abnormal results, were not referred for further evaluation and were therefore not receiving the necessary treatment. Inter-laboratory biochemical discrepancies and lack of population-specific reference ranges complicated the interpretation of results. The controversy surrounding whether, and how, to treat SCH influenced treatment practices.

Conclusions. Thyroid dysfunction is prevalent in South African children with DS. There is an urgent need to address the laboratory biochemical discrepancies, and to establish guidelines for surveillance and treatment to prevent further irreversible neurological and physical impairment.

S Afr Med J 2013;103(12 Suppl 1):966-970. DOI:10.7196/SAMJ.7111



Down syndrome (DS) (OMIM #190685) is the most common chromosomal abnormality observed in liveborn infants, and is the most frequent genetic cause of mental retardation. It is a congenital disorder caused by the presence of a third copy of the whole, or a critical part, of chromosome 21 (trisomy 21). Global live-birth rates for DS range between 1.5 per 1 000 (1 in 660 infants)^[1] and 1.2 per 1 000 (1 in 826 infants),^[2] with no predilection for race or socioeconomic group. Studies conducted in South Africa show a

DS prevalence of 1.8 and 2.09 per 1 000 live births in hospital-based studies in urban and rural populations, respectively.^[3,4]

DS is characterised by typical dysmorphic features, and is associated with an increased incidence of certain medical complications. The most common endocrine disorder associated with DS involves the thyroid gland.^[5] Individuals with DS exhibit a wide range of thyroid dysfunction. The forms of hypothyroidism found in individuals with DS include congenital hypothyroidism (CHT), subclinical or 'compensated' hypothyroidism (SCH), transient and primary hypothyroidism, central hypothyroidism, thyroxin-binding globulin deficiency and chronic lymphocytic thyroiditis.^[6] The diagnosis of hypothyroidism in DS is complicated by the overlap between thyroid-associated symptoms and clinical features of the syndrome (Table 1). Hyperthyroidism, although rarer, also occurs more frequently in DS individuals than in the general population.^[7]

In general, thyroid disorders have been reported to have a prevalence of 3 - 54% in people with DS, with the frequency of thyroid dysfunction increasing with age.^[8] It is estimated that the lifetime prevalence of hypothyroidism in DS is 30 - 50%.^[9] SCH is the most common form of thyroid dysfunction in DS, being reported in 25 - 32% of patients.^[10,11]

There are no recommended thyroid function test (TFT) reference ranges for children with DS, and doctors the world over have had to continue treating their patients with DS based on local reference ranges derived from studies on the general population.

It is a privilege for me to be first author of this contribution to Professor Jenkins' Festschrift. Optimising the care of children with Down syndrome has been a priority for the Division of Human Genetics since Professor Jenkins started the department in the 1970s. His legacy has continued to impact on how we view our role as medical geneticists who care for these children. A lot of Professor Jenkins' early work focused on DS, and my work is but one attempt to improve the care we provide. Although he was already officially retired when I joined the Division, he was always willing to share a kind word of advice and fascinating stories about the history of our profession. We often chatted in the corridor outside the office I occupied during the last two years of my registrar training, which just happened to be right next to his! (Shahida Moosa)

Table 1. Comparison of physical features in children with Down syndrome and hypothyroidism*

	Down syndrome	Hypothyroidism
Head	Brachycephaly, intermediate fontanelle	Normal
Tongue	Protruding	Large
Nasal bridge	Underdeveloped	Underdeveloped
Eyes	Upslanted palpebral fissures, epicanthic folds, Brushfield spots (in blue eyes)	Normal
Neck	Short	Short
Heart	Murmur (mainly atrioventricular canal defect)	Murmur (often nonspecific)
Abdomen	Umbilical hernia	Umbilical hernia
Neuromuscular	Hypotonia	Hypotonia
Skin	Dry	Dry
Extremities	Short hands and feet, transverse palmar crease, clinodactyly, wide sandal gaps, hyperextensible joints	Short hands and feet

* Adapted from Coleman.^[6]

In 1995, a consensus statement regarding optimal medical care for individuals with DS was drawn up by international experts.^[12] Several country-specific health surveillance protocols have subsequently been developed. The guidelines recommend regular screening programmes to identify treatable causes for a variety of symptoms, including hypothyroidism, which might otherwise be overlooked in patients with DS.^[13-15] As hypothyroidism impairs cognition and growth, and is treatable, early detection and treatment are essential in this already impaired population. In many parts of the world patients with DS have neonatal screening, as congenital hypothyroidism is one of the conditions included in newborn screening (NBS) programmes.

Despite these international DS thyroid screening recommendations, standardised biochemical treatment thresholds for DS do not exist. Doctors agree about the management of overt hypothyroidism (OHT) (increased thyroid-stimulating hormone (TSH) with low levels of free thyroxine (FT4)), and CHT especially carries a high risk of severe developmental delay if not treated promptly.^[16] Conversely, the management of SCH is surrounded by controversy.

SCH is frequently encountered in general paediatric practice, but its clinical significance is widely debated. There is currently no consensus with regard to: (i) the morbidity and clinical significance of SCH; (ii) whether to investigate individuals with SCH further; (iii) whether patients with SCH should be treated; and (iv) if they are treated, at which TSH levels treatment should be instituted.

There are a few reasons for the lack of consensus surrounding the management of SCH. Firstly, there is a paucity of data on the natural history of SCH in children. The concern is that, if left untreated, SCH would progress to OHT. As there is also a paucity of data derived from patients with DS, paediatricians currently extrapolate data from studies on normal children and normal adults, which may not be applicable to children with DS. Secondly, there are no large paediatric randomised controlled studies comparing outcomes in patients with SCH who were treated with thyroxine and those left untreated. Again, most clinicians rely on data from adult studies, which may also produce conflicting recommendations.

Many of the published guidelines only support treatment with thyroid hormone for patients with DS where the TSH level is greater than 10 μ IU/l. Most, such as those from the UK, do not support the treatment of SCH when a TSH level is less than 10 μ IU/l with normal FT4 values.^[13]

Proponents of treatment of SCH view it as a distinct and relevant entity to be treated. They suggest that decreased thyroid levels may

contribute to the poor growth and mental retardation in DS. Increased TSH levels reflect the sensitivity of the hypothalamic-pituitary axis to small decreases in circulating thyroid hormone. An FT4 level within the normal reference range may in fact be low for the particular patient, reflected as an increased TSH. Some researchers believe that SCH represents mild thyroid failure and should therefore be treated in most, if not all, cases.^[17] Papi *et al.*^[18] recommended that treatment be instituted in all newborns with SCH to prevent possible detrimental sequelae. Tüysüz and Beker^[11] recommend that every infant with DS be treated with thyroxine until the age of 3 years. They believe that this will prevent OHT in children with unstable thyroid function.^[11]

No standardised policy exists in South Africa with regard to thyroid function screening, testing or treatment in individuals with DS. None of the paediatric textbooks commonly used in South Africa mentions standard guidelines for the care of children with DS,^[19,20] despite the fact that the American Academy of Pediatrics first issued its DS guidelines in 2001.^[14] Lack of a standardised protocol means that even children born in a tertiary hospital may never have a TFT. Furthermore, South Africa does not have a national NBS programme. Congenital hypothyroidism is therefore not diagnosed in the critical, treatment-sensitive newborn period.

Children with DS form a substantial proportion of the patients seen at the three main genetic counselling (GC) clinics in the Greater Johannesburg area. In 2003, in line with international practice, clinicians in the Division of Human Genetics, National Health Laboratory Service (NHLS) and School of Pathology, University of the Witwatersrand, Johannesburg, decided to test the thyroid function of all children with DS seen at the GC clinics. Upon discharge from the clinics, all these children are issued with a referral letter recommending annual thyroid surveillance at their local hospitals.

This is the first study to formally audit this service and to document the range and prevalence of thyroid dysfunction in a cohort of South African children with DS. It is also a first attempt at describing the referral and treatment practices at two tertiary hospitals in Johannesburg.

Methods

The study was a retrospective, file-based audit of all the TFTs performed on children with DS at three selected academic hospitals. These hospitals, attached to the University of the Witwatersrand Medical School in the Greater Johannesburg area, were Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani

Baragwanath Academic Hospital (CHBAH) and Rahima Moosa Hospital (RMH). The subjects in the study were all patients with DS seen at one of the Division of Human Genetics' three main GC clinics at these hospitals. The 6-year time period under investigation was from the beginning of 2003 until the end of 2008. In total, 391 children were included in the study.

Most of the referral and treatment information was gathered from the GC files and the Paediatric Endocrine Clinic files from CMJAH and RMH. Little information was available regarding patients from CHBAH, as the Paediatric Endocrine Clinic files could not be accessed.

All TFTs performed on the patients with DS included in the study were considered valid for inclusion, unless they were performed at times of admission to hospital, during concurrent illness or within the first 48 hours after birth. Alterations in TFT results are common in the above situations, and can be misleading.^[16] In addition, TFT results were excluded if the patient was on thyroid hormone replacement therapy at the time of testing.

For the purposes of this study, we defined the various forms of thyroid dysfunction as outlined in Table 2 (all using the NHLS paediatric reference ranges).

Data were analysed using Statistica version 10. A difference between the results from CHBAH and the other two hospitals combined was statistically proven (data not shown). The TFT data from CHBAH were therefore analysed independently, while the data from CMJAH and RMH were analysed jointly. Non-parametric variables were described using medians and upper and lower limits. Logistic regression analysis was used to verify whether any of the demographic data had a significant influence on the TSH results. Throughout, a *p*-value of ≤ 0.05 was accepted as indicating statistical significance.

Ethics approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (certificate number M090710).

Results

Demographics

Of the 391 children with DS, 48.6% were seen at CHBAH. The majority of these children were black (92.1%), and there were equal numbers of males and females. Most of the patients were tested between the ages of 2 and 12 months (272/317; 85.8%), with few tests being conducted in the neonatal period (51/327; 15.6%) and in children over 5 years (3/327; 0.9%).

Number of patients tested and TFTs performed

Of the 391 patients in the study, 327 (83.6%) had at least one TFT. The remaining 64 patients (16.4%) had no TFT result. Of those with no result, 82.8% (53/64) had never had a TFT, and 17.2% (11/64) either had a failed phlebotomy attempt or insufficient blood submitted for analysis. Numbers of tests, by individual hospital, are shown in Table 3. From these 327 patients, a total of 536 TFT results were collected and 516 were suitable for further analysis. More than half of all TFTs were requested by the doctors at the GC clinics (54.0%), followed by the general paediatricians (35.5%) and other paediatric specialists (10.5%).

Thyroid dysfunction spectrum

As 516 results were collected from 327 patients, several patients clearly had more than one TFT. For clarity, the results are presented in terms of number of abnormal TFT results, and then number of actual affected patients. When patients were found to have more than one result, the assignment of thyroid function category relied on the initial test result.

A wide spectrum of thyroid dysfunction was represented in this cohort, with the noticeable exception of hyperthyroidism. Results mostly reflected a euthyroid state (295/516; 57.2%), but a large proportion (148/516; 28.7%) fell into the SCH category. Table 4 summarises the results in the different thyroid function categories. Although only 51 children had a TFT during the newborn period, it is notable that 23.5% had CHT.

Referral, management and follow-up

At the Paediatric Endocrine Clinic at CMJAH, almost all patients with DS are placed on thyroid hormone supplementation, unless they are overtly hyperthyroid. At the Paediatric Endocrine Clinic at RMH, only patients with a TSH >10 μ IU/l are treated, unless there is significant clinical evidence to suggest hypothyroidism at lower TSH levels. In this cohort, all patients with OHT and TSH levels exceeding 10 μ IU/l referred to the endocrine clinics at RMH and CMJAH were on treatment. There were 39 patients with SCH and a TSH level >10 μ IU/l, 12 (30.8%) of whom were reportedly on thyroxine replacement treatment.

Non-referral of patients with OHT and CHT to the endocrine clinics ranged from a rate of 26.7% at CMJAH to 43.2% at CHBAH. Rates of non-referral for those with SCH ranged from 47.8% at CHBAH to 57.1% at RMH. Of the 12 neonates with CHT, at least a quarter were not referred for treatment during the neonatal period. The patients with further abnormal results (Table 4) were not referred for further assessment.

Few patients (11/327; 3.4%) had yearly TFTs. Regular annual tests were performed by the doctors in the GC clinics (6/11; 54.5%), at the endocrine or developmental clinic (3/11; 27.3%), or at a peripheral hospital (2/11; 18.2%). Some patients (10/327; 3.1%) had *ad hoc* TFTs performed, presumably when they accessed healthcare.

Differences observed between the hospitals

A difference between the medians of the TFTs from the three hospitals was anticipated, because they use different machines for TFT

Table 3. Patients tested

Hospital	TST result, n (%)	
	Available	None/not available
CHBAH (N=190)	165 (42.2)	25 (6.4)
CMJAH (N=131)	106 (27.1)	25 (6.4)
RMH (N=70)	56 (14.3)	14 (3.6)
Total (N=391)	327 (83.6)	64 (16.4)

TFT = thyroid function test; CHBH = Chris Hani Baragwanath Academic Hospital; CMJAH = Charlotte Maxeke Johannesburg Academic Hospital; RMH = Rahima Moosa Hospital.

Table 2. Operational definitions

Congenital hypothyroidism (CHT)	Any patient with a high TSH level demonstrated within the newborn period (first 2 - 28 days of life)
Subclinical hypothyroidism (SCH)	A high TSH level in the presence of a normal FT4 level
Overt hypothyroidism (OHT)	A high TSH level and a correspondingly low FT4 level
Hyperthyroidism	A low TSH level and a high FT4 level

TSH = thyroid-stimulating hormone; FT4 = free thyroxine.

Table 4. Summary of abnormal thyroid function test results and number of affected patients

Thyroid function category	n/N (%)	
	Abnormal results	Affected patients
Subclinical hypothyroidism	148/516* (28.7)	99/327† (30.3)
TSH >10 µIU/l	46/148 (31.1)	39/99 (39.4)
Congenital hypothyroidism	16/62 (25.8) results from newborns	12/51 (23.5) children tested
TSH >10 µIU/l	12/16 (75)	
Overt hypothyroidism	14/516 (2.7)	14/327 (4.3)
TSH >10 µIU/l	8/14 (57.1)	8/14 (57.1)
Hyperthyroidism	0/516 (0)	0/327 (0)
Increased FT4 with normal TSH	14/516 (2.7)	14/327 (4.3)
Isolated increased FT4	19/516 (3.7)	19/327 (5.8)
Increased TSH and FT4	12/516 (2.3)	12/327 (3.7)

TSH = thyroid-stimulating hormone; FT4 = free thyroxine.
 *Total number of results.
 †Total number of patients tested.

analysis. There was no difference between the hospitals with regard to other variables (age ranges, race stratification, gender stratification or chromosome results). Analysis of variance confirmed a statistical difference between CHBAH and the other two hospitals ($p < 0.05$), but not between CMJAH and RMH ($p > 0.05$). A single patient was tested at CHBAH and CMJAH, a week apart. Using the result from CHBAH, the child would have been classified as having SCH, but the repeat test at CMJAH was within normal limits for his age.

Discussion

This study highlights several important issues regarding the diagnosis, referral and management of children with DS and thyroid dysfunction.

Given the resource constraints placed on the healthcare system by the burden of diseases such as HIV and tuberculosis, an overall thyroid testing rate of 83.6% in this cohort is remarkable. The cohort displayed a similar spectrum of thyroid dysfunction to international cohorts, with SCH being the most common problem encountered. However, no children were found to be hyperthyroid in this study, probably because very few tests were conducted in older children.

Although most of the children in the study were tested, there was a less structured approach to referral of those with an abnormal TFT result. Lack of referral of these patients at all the tertiary hospitals resulted in patients remaining without adequate endocrine assessment and treatment. This included patients with a clear diagnosis of SCH, CHT or OHT. Additionally, patients with results suggestive of central hypothyroidism, or an inadequate response from the hypothalamic-pituitary-thyroid axis, went uninvestigated.

Failed phlebotomy or insufficient blood submitted for analysis resulted in 11 children not having a TFT result. All TFTs are performed on venous blood, usually obtained from a peripheral vein. Too little blood may be obtained when phlebotomy in children with DS is difficult because of their short necks and tendency to become overweight, and an expert phlebotomist is needed to perform the venepuncture in such cases. Alternatives to classic phlebotomy such as finger/heel prick tests are viable, especially for detecting hypothyroidism.^[21,22]

The lack of referral can partly be explained by the lack of a standardised guideline outlining the process for active thyroid surveillance of children with DS. To benefit the patient, testing, as the first step in the surveillance protocol, must be followed by appropriate referral and treatment.

Owing to lack of specific guidelines, clinicians are left to judge clinically when to institute thyroid replacement treatment, which, based on the DS phenotype, can prove problematic. The controversy surrounding SCH seemed to extend to the present study cohort as well. While the paediatric endocrinologists at the different hospitals agree that SCH is a true reflection of patients' thyroid status, they differ with regard to its appropriate management. Nevertheless, the two different approaches can each be justified.

Moreover, doctors are faced with the challenge of trying to interpret results from black African children, using reference ranges derived from a different ethnic population. The situation is even more complicated when those black African children also have DS.

The statistically significant difference observed between results from the CHBAH laboratory and the other hospitals also highlights the possibility that there may be significant inter-laboratory differences, adding to the difficulty of interpretation of TFT results.

Conclusion

Left untreated, hypothyroidism causes irreversible mental and physical handicaps. Early detection and treatment is therefore desirable, particularly in children who already have a predisposition to learning disabilities and growth impairment.

Optimising the care for children with DS should be prioritised. It is vital that a standardised, national surveillance protocol be established to specifically address the health needs of children with DS in South Africa, while taking into account the country's limited resources. The guidelines would need to include standardised nationwide protocols for thyroid surveillance. Ideally this would include TFT testing for all newborns with DS, annual thyroid surveillance of all children with DS, active and appropriate referral for monitoring and treatment, less invasive testing techniques, and the facilities to have these tests and treatment as close to home as possible. The guidelines would preferably be implemented in the primary or secondary hospital systems.

However, the immediate implementation of such guidelines is hampered by several issues. The first is the discrepancy between the laboratories noted in this study. Urgent studies are needed to delineate the exact causes of the differences. Alternative testing methods, such as heel prick tests, should be optimised as a matter of urgency. Whether establishing DS-specific TFT reference ranges would prove beneficial in the South African healthcare setting also requires further consideration.

Secondly, the absence of an NBS policy in South Africa means that children with DS who have CHT are not being diagnosed during the

neonatal period, which is the ideal time to institute treatment. Instituting a national NBS to test for thyroid dysfunction will benefit not only newborns with DS, but the general population of neonates as well.

Without the abovementioned prerequisites, national DS surveillance guidelines would be of little practical value. It is hoped that the results of this study will increase awareness of the current challenges and form the basis for discussion around the management and care of children with DS in South Africa, finally leading to more structured protocols regarding health screening and treatment of complications associated with DS.

Acknowledgements. The authors thank Dr Ajay Chiba (RMH) for his help and support for this project and Professor Jennifer Kromberg (Division of Human Genetics, NHLS and University of the Witwatersrand and SM's Mellon Mentor) for her guidance and encouragement. This study formed the basis of an MMed (Medical Genetics) research report submitted by SM to the University of the Witwatersrand.

References

1. Penrose LS, Smith GE. Down's Anomaly. Boston: Little Brown, 1966.
2. Hook EB. Chromosome abnormalities: Prevalence, risks and recurrence. In: Brock DLH, Rodeck CH, Ferguson-Smith MA, eds. Prenatal Diagnosis and Screening. Edinburgh: Churchill Livingstone, 1992:351-392.
3. Venter PA, Christianson AL, Gericke GS, et al. Congenital anomalies in rural Black South African neonates – a silent epidemic? *S Afr Med J* 1995;85(1):15-20.
4. Christianson AL. Down syndrome in sub-Saharan Africa. *J Med Genet* 1996;33(2):89-92. [http://dx.doi.org/10.1136/jmg.33.2.89]
5. Pueschel SM, Jackson IMD, Giesswein P, Dean MK, Pezzullo JC. Thyroid function in Down syndrome. *Res Dev Disabil* 1991;12(3):287-296. [http://dx.doi.org/10.1016/0891-4222(91)90013-1]
6. Coleman M. Thyroid dysfunction in Down syndrome: A review. *Down Syndrome Research and Practice* 1994;2(3):112-115. [http://dx.doi.org/10.3104/reviews.40]
7. Takahashi H, Bordy MD, Sharma V, Grunt JA. Hyperthyroidism in patients with Down's syndrome. *Clin Pediatr* 1979;18(5):273-275. [http://dx.doi.org/10.1177/000992287901800503]
8. Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Annérén G. Thyroid dysfunction in Down's syndrome: Relation to age and thyroid autoimmunity. *Arch Dis Child* 1998;79(3):242-245. [http://dx.doi.org/10.1136/ad.79.3.242]
9. Prasher VP, ed. Down syndrome and Alzheimer's disease: Biological correlates. Abingdon, Oxon: Radcliffe Publishing, 2006.
10. Rubello D, Pozzan GB, Casara D, et al. Natural course of subclinical hypothyroidism in Down's syndrome: Prospective study results and therapeutic considerations. *J Endocrinol Invest* 1995;18(1):35-40.
11. Tüysüz B, Beker DB. Thyroid dysfunction in children with Down's syndrome. *Acta Paediatr* 2001;90(12):1389-1393. [http://dx.doi.org/10.1111/j.1651-2227.2001.tb01601.x]
12. Pueschel SM, Annérén G, Durlach R, Flores J, Sustrová M, Verma IC. Guidelines for optimal medical care of persons with Down syndrome. International League of Societies for Persons with Mental Handicap (ILSMH). *Acta Paediatr* 1995;84(7):823-827. [http://dx.doi.org/10.1111/j.1651-2227.1995.tb13768.x]
13. Down Syndrome Medical Interest Group (UK). Basic medical surveillance essentials for people with Down syndrome-thyroid. 2005. <http://www.dsmig.org.uk/library/articles/guideline-thyroid-6.pdf> (accessed July 2011).
14. Cunniff C, Frias JL, Kaye C, Moeschler JB, Panny SR, Trotter TL. Health supervision for children with Down syndrome. *Pediatrics* 2001;107(2):442-449. [http://dx.doi.org/10.1542/peds.107.2.442]
15. Bull MJ. Health supervision for children with Down syndrome. *Pediatrics* 2011;128(2):393-406. [http://dx.doi.org/10.1542/peds.2011-1605]
16. Rossi WC, Caplin N, Alter CA. Thyroid disorders in children. In: Moshang T, ed. *Pediatric Endocrinology: The Requisites in Pediatrics*. St Louis, Miss.: Elsevier Mosby, 2004:171-190.
17. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab* 2001;86(10):4585-4590. [http://dx.doi.org/10.1210/jc.86.10.4585]
18. Papi G, Uberti ED, Betterle C, et al. Subclinical hypothyroidism. *Curr Opin Endocrinol Diabetes Obes* 2007;14(3):197-208. [http://dx.doi.org/10.1097/MED.0b013e32803577e7]
19. Kliegman RM, Behrman RE, Jenson HB, Stanton BMD. *Nelson Textbook of Pediatrics*, 18th ed. Philadelphia: WB Saunders, 2007.
20. Wittenberg DF, ed. *Coovadia's Paediatrics and Child Health*. 6th ed. Cape Town: Oxford University Press Southern Africa, 2009.
21. Noble SE, Keyland K, Findlay CA, et al. School based screening for hypothyroidism in Down's syndrome by dried blood spot TSH measurement. *Arch Dis Child* 2000;82(1):27-31. [http://dx.doi.org/10.1136/ad.82.1.27]
22. Murphy J, Philip M, Macken S, et al. Thyroid dysfunction in Down's syndrome and screening for hypothyroidism in children and adolescents using capillary TSH measurement. *J Pediatr Endocrinol Metab* 2008;21(2):155-163. [http://dx.doi.org/10.1515/JPEM.2008.21.2.155]

Accepted 6 July 2013.