Radioactive Iodine-131 as a Definitive Treatment in Rare Association of Down Syndrome With Hyperthyroidism: A Case Report and Review of Literature

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Abstract

Down syndrome characterized by trisomy of chromosome 21 is frequently associated with thyroid dysfunctions due to underlying autoimmune disorders. Hypothyroidism is the commonest thyroid dysfunction and hyperthyroidism, usually Graves' disease, is far less common. On literature review, we came across approximately 112 cases reported so far with the first such case report in 1946. The published data from India on hyperthyroidism in Down syndrome is of three case reports. We report one such patient, an adult male of 28 years who was administered Iodine-131 as a definitive treatment after 9-10 years of initial diagnosis.

Key words: *Down syndrome, hyperthyroidism, iodine-131*

Introduction

Down syndrome (DS) described by John Langdon Down, a British physician in 1866, is characterized by the common chromosomal disorder of trisomy at chromosome 21 with mental deficiency of varying grades in addition to other ailments and abnormalities.[1] The reported incidence of DS from various countries varies from 1/449 to 2/700 of live births and hypothyroidism in DS due to autoimmune thyroid disease is the commonest thyroid dysfunction having reportedly a high approximate prevalence of 50%.[2,3] Hyperthyroidism mostly Graves' disease in DS is less common with a prevalence of less than 3%.[4] The first such case was published in 1946 by Gilchrist.[5] The reported worldwide literature on hyperthyroidism in DS is that of about 112 sporadic cases with only three to four cases from India. We describe one such case in an adult male of DS with hyperthyroidism (Graves' disease) who was administered oral Iodine-131 as a definitive treatment.

Case Report

A 28-year-old adult male of DS with hyperthyroidism was referred to our department for Iodine-131 treatment. History of the patient revealed that at 19 years of age this patient of DS had complaints of increased frequency of stools, heat intolerance, and increased sweating. On the basis of his clinical profile and laboratory investigations, he was diagnosed with associated hyperthyroidism. He was prescribed antithyroid drug carbimazole and continued to be on endocrinology follow-up for 9 years. The clinical records of the patient confirmed an irregular compliance to antithyroid medication and repeated relapses of hyperthyroidism. At presentation in our department, the patient was conscious, cooperative, and well-oriented in time, space, and person. His height was 157 cm and he weighed 63 kg. He had a chubby appearance with slanted eyes and a short neck. His extremities were short. The nasal bridge was undeveloped. He did not have any tremors and the skin over the palms was dry and warm. He had normal blood pressure with a regular good volume radial pulse of 72 beats/min. On neck examination, there was no visible swelling; however, on palpation the thyroid gland was found to be diffusely enlarged with firm consistence and moving freely on deglutition .There was no bruit over the gland and the margins were well-delineated. There was no lymph node enlargement in the neck. The systemic clinical examination and echocardiography were normal. Prior to

How to cite this article: Khan SH, Mahajan A, Rather TA. Radioactive Iodine-131 as a definitive treatment in rare association of down syndrome with hyperthyroidism: A case report and review of literature. Indian J Nucl Med 2017;32:19-24.

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Access this article online

Website: www.ijnm.in

DOI: 10.4103/0972-3919.198458

Quick Response Code:

scheduling the patient for Iodine-131 treatment a laboratory workup was advised after stopping the antithyroid drug carbimazole for 5 days. During this period he was prescribed oral β-blocker propranolol in divided doses. The thyroid function tests revealed tri-iodothyronine [T3] of 2.7 ng/mL [ref range 0.70-2.50], tetra-iodothyronine [T4] of 14.99 µg/dL [ref range 4.00-13.00] and thyroid stimulating hormone (TSH) of 0.06 µIU/mL [ref range 0.50-6.5]. A Technetium 99m pertechnetate thyroid scan done after 15 minutes of 5 mCi intravenous injection revealed diffusely enlarged thyroid gland with uniformly intense tracer uptake. The 99m Technetium pertechnetate uptake was elevated at 53% [normal range 0.4-6%]. Scan appearance and uptakes were reported as consistent with Graves' disease [Figure 1]. A subsequent 2 and 24 hours Iodine-131 thyroid uptake after oral administration of 25 µCi of Iodine-131 was elevated at 29.3 and 67.4%, respectively. His thyroglobulin and antithyroid peroxidase levels were elevated at 472 ng/mL [ref range 0.00-37] and 702 IU/mL [ref range 0.0-9.0], respectively. Chromosomal karyotyping confirmed 46, XY, der [21; 21] [q10; q10], +21 DS [Figure 2]. The patient was administered a fixed oral dose of 10 mCi [370 MBq] of Iodine-131 on an empty stomach. Two months later his T3 level normalized to 0.86 ng/mL, T4 to 7.61 µg/dL TSH was 0.09 µIU/mL. However, at 4 months after Iodine-131 treatment patient became hypothyroid with a TSH level greater than 100 µIU/mL. He was prescribed a daily substitution dose of 125 µg of oral thyroxine. On

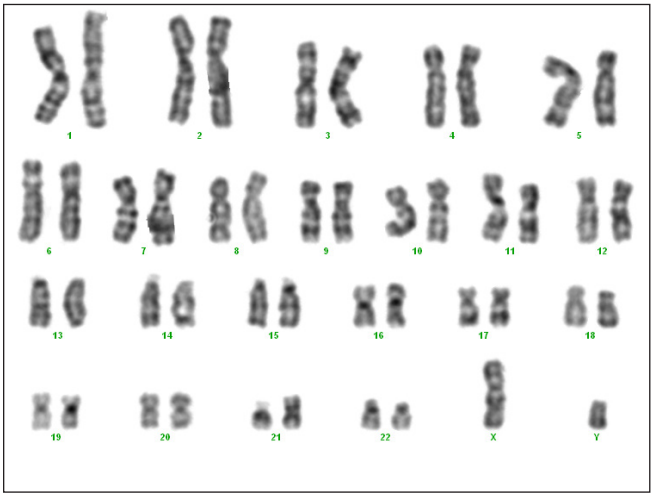

Figure 1: Chromosomal karyotyping showing 46, XY, der (21; 21) (q10; q10), +21 Down syndrome.

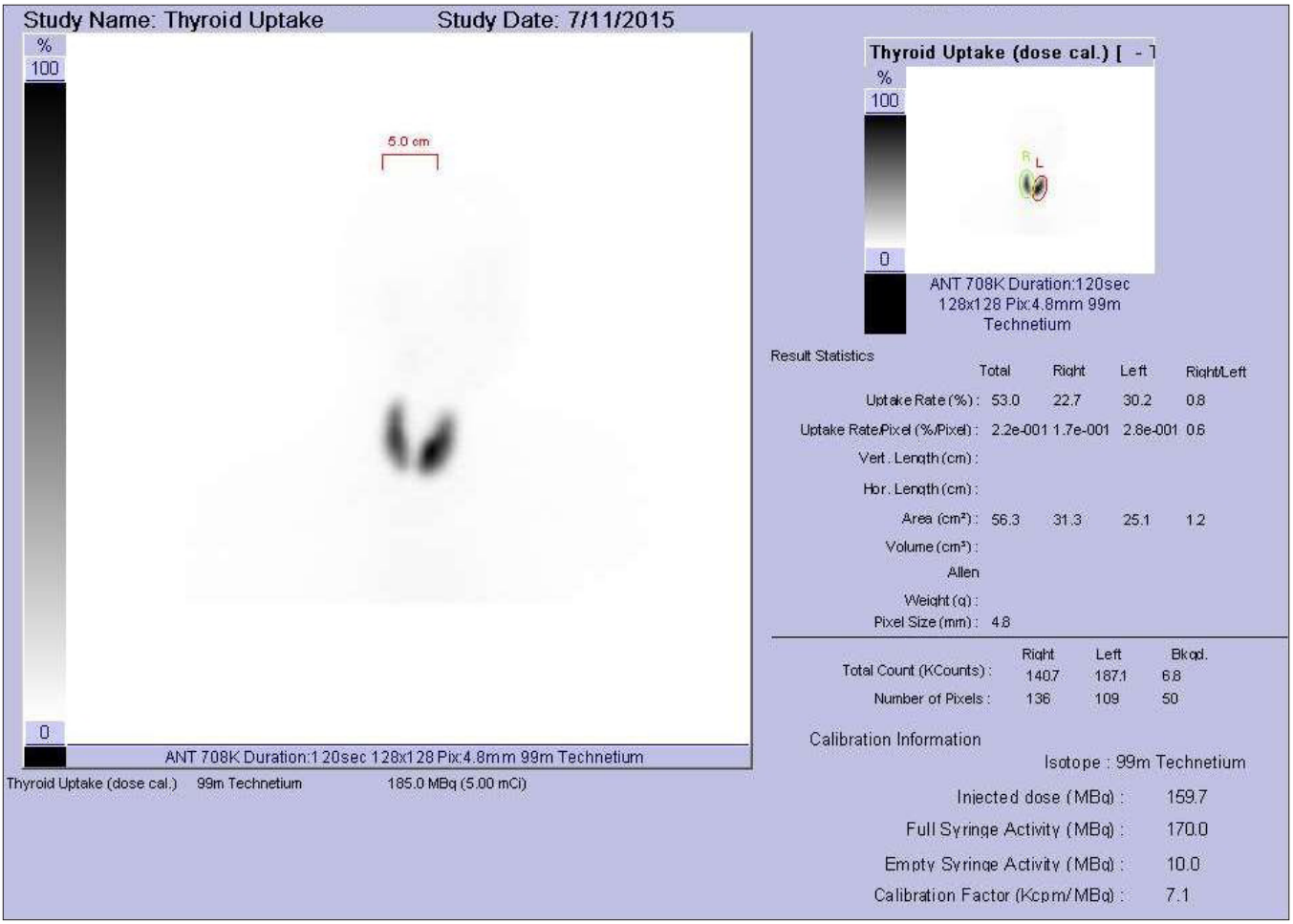

Figure 2: Tc-99m thyroid scan with uptakes at 15 minutes postinjection

his last follow-up at 9 months after Iodine-131 treatment he is relieved of his thyrotoxic symptoms with a weight gain of 8 kg and normalized thyroid hormone levels of T3, T4, and TSH at 1.13 ng/mL, 12.81 µg/dL, 0.50 µIU/mL, respectively.

Discussion and Review of Literature

Hypothyroidism of autoimmune etiology is the commonest thyroid dysfunction in DS. Prevalence of hyperthyroidism in DS is reportedly far less. The incidence of thyroid dysfunction in DS increases from 0.7% in infants to 12% by adulthood.[6] Neonatal screening program for detecting congenital hypothyroidism has greatly improved the detection of hypothyroidism including the one associated with DS, which otherwise have considerable overlap of signs and symptoms. Association of hyperthyroidism with DS though reportedly under 3% has relatively a higher prevalence among DS than the general population. On bibliographic review approximately 112 patients of DS with hyperthyroidism are documented with the two recently published large series of 28 and 12 patients from Italy and Spain, respectively.[3,7] In the majority of these patients the diagnosis was made in childhood and the patients appear to have almost equal gender distribution. Autoimmune Graves' disease is the etiology in most of the reported cases. Published literature from India is scanty and documents only four cases including this case report of hyperthyroidism in DS.[8-10] In a published Indian study of 300 children with DS from 2004 to 2014, 82 patients were found to have abnormal thyroid hormone profiles with 76 patients having subclinical hypothyroidism and the rest overt hypothyroidism.[11] No patient in this review study was found to have hyperthyroidism. From the limited data available from India it appears that the patients of DS with hyperthyroidism from India are younger and do not show any gender predilection.[8-10] This observation is consistent

Table 1: Down syndrome associated with hyperthyroidism (review of literature, 1946–1986)

S No	Author	Year	No of cases (gender)	Population (age years gender)	Etiology	Initial Treatment	Definitive treatment
1	Gilchrist[5]	1946	1	Adult (22 F)	-	-	-
2	Mc Girr[19]	1956	1	Adult (23 F)	-	-	-
3	Esen[21]	1957	1	Children (15 F)	-	-	-
4	Dupuy[22]	1957	1	Children (15 F)	-	-	-
5	Diggle[23]	1958	1	Children (6 F)	-	-	-
6	Nickey[24]	1960	1	Children (12 F)	-	-	-
7	Abrahamsen[25]	1961	2	Adults (21 F,41 F)	-	-	-
8	Johnson[26]	1962	2	Children and adult (14 F, 36 M)	-	-	-
9	Timbury[27]	1963	1	Adult (29 F)	-	-	-
10	Kay[28]	1963	2	Children (9 F, 13 F)	-	-	-
11	Hayles[29]	1965	1	Children (14 F)	-	-	-
12	Ansari[30]	1967	1	Adult (26 F)	-	-	-
13	Subrt[31]	1968	1	Children (6 M)	-	-	-
14	Aarskog[32]	1969	1	Children (7 F)	-	-	-
15	Hollingworth[33]	1974	2	Children and adult	-	-	-
16	Azizi[34]	1974	1	Children (11 F)	-	-	-
17	Baxter[13]	1975	1	-	-	Carbimazole	-
18	Murdoch[35]	1977	1	-	-	-	-
19	Morton[36]	1978	1	Children (10 F)	-	-	-
20	Takahashi[37]	1979	1	Children (12 F)	-	-	-
21	Mc Culloch[14]	1983	1	Adult	Graves'	Carbimazole	Iodine-131
22	Fort[4]	1984	3	Children	Graves'	-	-
23	Loudon[38]	1985	1	Children	-	-	-
24	Cutler[15]	1986	1	Children	Graves'	PTU	No
25	Nibhanupudy[39]	1986	1	Adult (27 F)	-	-	-

F = Female, M = Male, PTU = propylthiouracil.

Table 2: Down syndrome associated with hyperthyroidism (review of literature, 1987 - 2016)

S No	Author	Year	No of Cases (Gender)	Population (age years gender)	Etiology	Initial Treatment	Definitive Treatment
1	Blumberg[40]	1987	1	Children (13 M)	-	-	-
2	Zori[3]	1990	5	Children and Adults	3 Thyroiditis,2	-	-
3	Dinani[41]	1990	1	Adult	-	-	-
4	Pozzan[42]	1990	2	Children and adult	Graves'	-	-
5	Pueschel[43]	1991	1	Children	-	-	-
6	Colombo[44]	1992	1	Children and adult	Transient	-	-
7	Tambyah[45]	1993	2	Adult	Graves'	-	-
8	Crespo[46]	1996	1	Children (8 F)	-	-	-
9	Sridhar[9]	1997	1	Children (F)	-	-	-
10	Bhowmick[16]	1997	5 (4 F,1 M)	Children	Graves'	PTU	-
11	Karlsson[47]	1998	2	Children	-	-	-
12	Castro Lobera[48]	1999	2	Children and adult	-	-	-
13	Sanz[17]	1999	3	Adults	Graves'	PTU	Iodine-131 (2)
14	Ali[49]	1999	1	Adult and children	-	-	Iodine-131
15	Gruneiro de[50]	2002	4	Children	Graves'	-	-
16	Soriano Guillen[18]	2003	3	Children	Graves'	Methimazole	No
17	Dias[2]	2005	1	Children	-	-	-
18	Ahluwalia[8]	2005	1	Children (M)	-	Carbimazole	-
19	Chemli[51]	2006	1	Children	-	-	-
20	Sahin[20]	2006	1	-	Graves'	Carbimazole	Surgery
21	Goday Arno[12]	2009	12 (7F,5M)	Children and adults	Graves'	Carbimazole	Iodine-131(12)
22	Bhat[10]	2010	1	Children (7 F)	Graves'	Carbimazole	-
23	De Luca Filippo[7]	2010	28 (14 F,14 M)	Children and adults	Graves'	Carbimazole	-
24	Present case report	2016	1	Adult (19 M)	Graves'	Carbimazole	Iodine-131

F = Female, M = Male, PTU = propylthiouracil.

with that of the largest published Italian and Spanish series. Considering the 1/449 to 2/700 incidence of DS among the live births the total burden of DS with thyroid dysfunction including hyperthyroidism is likely to be higher in India. Less documentation could be attributed to under diagnosis due to limited access to health care in the remote areas. Overlapping symptoms and social dimensions of DS also complicate the documentation of thyroid dysfunctions in DS. The available literature review of treatment preference in 57 cases of hyperthyroidism associated with DS shows conflicting results. In the largest multi-institutional Italian study based on 28 patients of DS with Graves' disease, no patient required nonpharmacological treatment like Iodine-131 or surgery during the follow-up period of 4.0 ± 2.8 years after the first cycle of methimazole was continued for an average period of 2.8 ± 1.6 years.[7] On the contrary, in the earlier Spanish study based on 12 patients of DS with Graves' disease all the patients' eventually required definitive treatment with Iodine-131 due to shorter remissions on carbimazole.[12] On overall review of 58 cases with available treatment details, Iodine-131 was administered as a definitive treatment in only 16 [27.58%] patients [Tables 1 and 2].[7] In view of the mental profile of patients with DS, the presumable reluctance in using Iodine-131 as a definitive treatment for reasons of patient cooperation and related issues of radiation safety are understandable. Arguably an upfront (mostly onetime) Iodine-131 therapy seems to be a better option for such patients likely to have issues related to compliance and frequent relapses on long-term medication with conventional antithyroid pharmacological drugs. Iodine-131 treatment doses for hyperthyroidism particularly for patients with special needs like DS is available in capsule packages, which are very convenient to swallow on an outpatient protocol. The patient described in this case report was referred to our department after a long period of noncompliant treatment and repeated relapses on antithyroid drug carbimazole. During the period that he was on antithyroid drug carbimazole, he continued to have toxic symptoms of various grades for reasons of noncompliance and shorter remission periods of 3–4

months after withdrawal. In the reported Spanish series of 12 patients, no patient achieved remission longer than 6 months after carbimazole withdrawal and eventually all such patients who relapsed were given Iodine-131. In the long run, Iodine-131 treatment works out more convenient and economical. Over a period of 6-12 weeks post Iodine-131 oral administration our patient was relieved of all his thyrotoxic symptoms and his thyroid function parameters were within normal limits. Expectedly, he developed a mild form of post Iodine-131 hypothyroidism, which was easily managed with oral thyroxine.

Functional disorders of thyroid gland are relatively more common in patients of DS and as such screening of all such neonates with standard thyroid function tests at birth and subsequently till the adulthood must be incorporated in the standard management protocol. Hyperthyroidism associated with DS can be managed conveniently and definitively by an early administration of radioactive Iodine-131. India needs to compile a comprehensive database for DS including the thyroid function among such patients. This would be possible through a well-coordinated multi-institutional effort under the auspices of a national health care program. Based on the observations, a strategy for early diagnosis and treatment of associated thyroid dysfunctions in DS can be formulated to reduce the scale and duration of morbidity in such patients.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflicts of interest

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