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ORIGINAL ARTICLE

Thyroid dysfunction due to ^{131}I-metaiodobenzylguanidine in patients with neuroblastoma

Disfunción tiroidea por I^{131}-Metayodo Benzilguanidina en pacientes con neuroblastoma

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What do we know about the subject matter of this study?

In patients with neuroblastoma, thyroid dysfunction following I^{131}-MIBG therapy is a common complication. Inadequate follow-up can have serious consequences, including neurodevelopmental delay.

What does this study contribute to what is already known?

The frequency of hypothyroidism after I^{131}-MIBG therapy was 56%. Thyroid profile should be performed twice a year and evaluated annually by a pediatric endocrinologist during the first 5 years after the diagnosis of neuroblastoma.

Abstract

The treatment of advanced neuroblastoma includes chemotherapy, surgery, and radiotherapy with 131-I-Metaiodobenzylguanidine (131-I-MIBG). Despite strategies to protect thyroid function, its dysfunction is reported between 12 and 85%. **Objective:** To identify the frequency of thyroid dysfunction in cases of neuroblastoma treated with 131-I-MIBG. **Patients and Method:** Cross-sectional study. We included all the cases with neuroblastoma treated with 131-I-MIBG between 2002 and 2015, with complete somatometry, and complete thyroid profile (TSH, free and total T3 and T4, and anti-thyroglobulin and antiperoxidase antibodies). **Results:** 27 patients were identified out of which eleven died (40%). Out of the 16 surviving cases, 9 (56%) presented thyroid dysfunction: 2 (13%) cases with subclinical hypothyroidism and 7 (44%) cases with clinical hypothyroidism (3 cases due to psychomotor developmental delay and 4 due to growth deceleration). The patients presented clinical manifestations at 16.1 months (1.2-66.3 months) after receiving the radiopharmaceutical at a

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cumulative dose of 142 mCi (96-391.5 mCi). No differences were found in the age at diagnosis, age at the start of treatment with 131-I-MIBG, the cumulative dose of 131-I-MIBG, and the time elapsed between the dose and the thyroid profile among the cases with or without thyroid dysfunction. **Conclusions:** 56% of patients with neuroblastoma had thyroid dysfunction. Most of the cases with hypothyroidism were referred when thyroid dysfunction was clinically evident. A thyroid profile should be performed every 6 months, along with an annual endocrinological evaluation during the next 5 years in these patients.

Introduction

Neuroblastoma is an embryonal tumor of the peripheral sympathetic nervous system. It is the most common extracranial solid tumor in children and shows a very heterogeneous biological and clinical behavior[1].

Worldwide, it presents an incidence of 7 to 14 cases per million children per year[2], whereas in Mexico between 1995 and 2005, it was reported an incidence of 3.8 cases per million children per year in a population with health insurance[3]. In 80% of the cases the age at presentation is under 4 years[2,4].

In a study conducted in Mexico between 1996 and 2001, it was determined that 70% of patients admitted with neuroblastoma presented advanced stages (III and IV) at diagnosis, with a survival of 27% at 5 years[5].

Treatment for advanced stages is multidisciplinary, including chemotherapy, surgery, radiation therapy, and I^{131}-metaiodobenzylguanidine (I^{131}-MIBG) therapy[6], a radioisotope used for diagnostic and therapeutic purposes[6,7].

MIBG is a guanethidine derivative and a norepinephrine analog with specific affinity towards the cells in the neural crest. Neuroblastoma cells express the norepinephrine transporter. Hence, when MIBG is marked with Iodine-^{131}, neuroblastoma cells are selectively targeted and destroyed by the radioisotope, adding effectiveness to the induction, consolidation, and relapse chemotherapy regimens[8,9] with response rates for refractory disease that range from 20% to 40%[7].

This radiopharmaceutical has presented short- and long-term adverse effects such as nausea, vomiting[10], hepatotoxicity[11], myelotoxicity, thyroid dysfunction, and second neoplasms[14].

The thyroid dysfunction after I^{131}-MIBG treatment ranges from 12% to 85%, depending on the therapeutic protocols and the grade of blockage of thyroid function[12,15-17]. Multiple studies have shown that, despite performing thyroid blockage with oral stable iodine, thyroid dysfunction presents a high incidence[15].

Patients with neuroblastoma have factors inherent to the treatment received (chemotherapy, radiotherapy, I^{131}-MIBG therapy) that increase the risk of thyroid disease, therefore, the early identification of the dysfunction is essential for hormone replacement and follow-up.

In addition, the risk of developing a second malignancy, such as leukemia, thyroid cancer, rhabdomyosarcoma, or schwannoma, is 20% higher than the general population and they can occur up to 10 years later[14].

There are very few studies reporting the incidence of thyroid dysfunction in patients with neuroblastoma and their results are highly variable. Therefore, the objective of our study was to identify the frequency of thyroid dysfunction in neuroblastoma patients who received I^{131}-MIBG at therapeutic doses.

Patients and Methods

Design

Between January 2012 and December 2015, we conducted a cross-sectional study in a tertiary referral pediatric hospital. We identified in the hospital database all pediatric patients with neuroblastoma who were diagnosed according to the histopathological study performed at disease onset and that received I^{131}-MIBG as part of their treatment in January 2012 to December 2015 period. Patients with incomplete biochemical studies or who did not agree to participate in the study were excluded. From the medical record, we registered the date of diagnosis, age, initial anthropometry measurement, stage of neuroblastoma, cumulative dose of I^{131}-MIBG, and hormonal studies performed.

In those patients who did not have a thyroid profile after the administration of I^{131}-MIBG, a complete physical examination and thyroid profile was performed during the study period.

Chemotherapy protocol

The chemotherapy regimen included Cyclophosphamide and Epirubicin, alternated with Cisplatin, Ifosfamide, and Etoposide every 3 weeks for a period of 12 months. No patient received cranial radiotherapy. After completing 6 cycles of chemotherapy, the therapeutic dose of I^{131}-MIBG was administered at 100 to 150 mCi/dose. Two days before the ad-

ministration of I^{131}-MIBG, the patient was prescribed a 1% lugol solution, one drop per kilogram of body weight per day, with a maximum of 40 drops per day, divided into 2 doses, which continued for 5 days after the administration of I^{131}-MIBG therapeutic dose.

Measurement of blood thyroid hormone levels

Through venipuncture sampling, serum thyroid hormone levels were collected between 7 and 8 hours in the morning after 12 hours of fasting. Using electrochemiluminescence immunoassay (ECLIA), the following levels were measured: thyroid-stimulating hormone (TSH), total and free triiodothyronine (T3 - FT3), and total and free thyroxine (T4 - FT4). The cobas® 6000 analyzer e601 module (Roche Diagnostics GmbH, Indianapolis, IN, USA) was used according to the manufacturer's recommendations. The intra- and inter-assay coefficients of variation for all measurements were < 7%. A standard curve was included in each test.

Diagnosis determined by hormone profile

We defined subclinical hypothyroidism as having high TSH blood levels (between 6 mu/ml and 9.9 mu/ml) and normal serum levels of thyroid hormones; and hypothyroidism as having serum levels of TSH > 10 mu/ml and normal or low serum levels of thyroid hormones.

Statistical analysis

We calculated median, minimum, and maximum for the quantitative variables, and for the qualitative oneswe used percentages and frequencies. Mann Whitney's U was applied to estimate the difference of quantitative variables between patients with and without thyroid dysfunction. $P < 0.05$ was considered statistically significant. STATA v.12.0 software was used for statistical analysis.

Ethical aspect

The protocol was approved by the Hospital's Research and Ethics Committee. The parents signed the informed consent and, if patients were over 8 years old, they signed informed assent according to the recommendations of the Declaration of Helsinki.

Results

We identified 27 patients, with a median age at diagnosis of neuroblastoma of 8 years (minimum age 1 month and maximum 12 years 9 months). At the time of diagnosis, 33% were in stage III and 67% in stage IV (Table 1).

Regarding the administration of I^{131}-MIBG, the median age of patients receiving the first dose was 3.6 years (minimum 8 months, maximum 13 years). Out of the total patients, 13 (48%) received a single dose of I^{131}-MIBG, 7 (26%) received two doses, 5 patients (19%) received three doses, and 1 patient (4%) received four doses, resulting in a cumulative median dose of 116 mCi (minimum 84, maximum 392 mCi). Out of the 27 patients who received the I^{131}-MIBG, 11 (41%) died, with a median survival of 14 months at a 5-year follow-up, 6 patients died in the first year of diagnosis, and 5 at three years of follow-up (Table 1).

Out of the 16 surviving patients, 8 had no post-I^{131}-MIBG thyroid function tests, thus they were scheduled for laboratory studies and clinical evaluation. 9 of the 16 (56.2%) patients presented an abnormal thyroid profile, which was performed at a median of 16 months after the I^{131}-MIBG dose (minimum 1 month, maximum 66 months). The median age at treatment was 3 years (minimum 9 months, maximum 7 years). The median cumulative dose of I^{131}-MIBG was 142 mCi, minimum 96 mCi and maximum 392 mCi (Table 2).

All patients presented hypothyroidism, with a median TSH of 75 mU/l (minimum 13.7 and maximum 605). Anti-peroxidase and anti-thyroglobulin antibodies were negative in all of them.

The 7 survivor euthyroid patients (43.8%) had their thyroid profiles done at 40 months (minimum 14, maximum 100) after the I^{131}-MIBG dose. The median cumulative dose was 216 mCi, with a minimum of 84 mCi and a maximum of 223 mCi (Table 2).

Seven out of the 9 children with thyroid dysfunction presented clinical manifestations before the biochemical diagnosis of hypothyroidism, 3 with delayed psychomotor development, and 4 with stunted growth.

We compared the age at diagnosis of neuroblastoma, the age at the beginning of treatment with I^{131}-MIBG, the cumulative dose of I^{131}-MIBG, and the time elapsed between dose and thyroid profile, without finding statistical differences between cases with or without thyroid dysfunction (Table 2).

Table 1. Demographic, diagnostic and treatment characteristics of children with neuroblastoma who received I^{131}-MIBI

	All (n = 27)	Surviving patients (n = 16)
	Median (min-max)	
Age at diagnosis (years)	2.8 (0-12)	3.6 (0-12)
Male*	10 (37%)	8 (50%)
Neuroblatoma stage IV*	18 (66%)	10 (62%)
Age at treatment (years)	3.6 (0-12)	2.6 (0-12)
Cumulative dose of I^{131}-MIBI (mCi)	116 (84-392)	173 (84-392)

*n (%)

Table 2. Comparison between surviving patients with and without thyroid dysfunciton

	Hypothyroidism (n = 9)	Euthyroid (n = 7)	p
	Median (min-max)		
Age at diagnosis (years)	3 (1 mes -6)	9 meses (1 mes -12)	0.25
Age at treatment (years)	3 (9 meses -7)	1 (9 meses-12)	0.59
Cumulative dose of I^{131}-MIBI (mCi)	142 (96-391)	216 (84-223)	0.79
Time between dose and thryoid profile (months)	16 (1-66)	40 (14-100)	0.086
Thyroid stimulating hormone (mU/l)	75 (13.7-605)	3.2 (1.51-4.2)	-

Discussion

In our study, we observed that half of the patients with neuroblastoma had thyroid dysfunction and 19% presented neurodevelopmental delay due to a late diagnosis of hypothyroidism.

MIBG does not cause any adverse effect on the thyroid gland, but I^{131} does. I^{131}-MIBG is excreted almost entirely in urine, however, a percentage is metabolized by the liver and produces free I^{131}. Consequently, the thyroid will also concentrate radioactive iodine that will lead to thyrocyte destruciton and increase risk of thyroid tumors[19].

Hence the importance of protecting the thyroid gland by administering high doses of oral stable iodine which stimulates the Wolff-Chaikoff effect[20,21]. The Wolff-Chaikoff effect is a self-regulatory mechanism of the thyroid gland when there is a sudden increase in the availability of circulating iodine, causing suppression in the response of the thyroid cells to TSH, decreasing the synthesis of thyroglobulin, its iodization and the release of thyroid hormones[21].

The recommendations for the management of patients with neuroblastoma treated with I^{131}-MIBG include the administration of oral stable iodine, two days before and up to 10 days after[22]; however, our patients were only treated for 5 days, similar to other case series[11,12,15-17,23-25]. Even though the thyroid gland was protected in some degree, we detected 56% of frequency of thyroid dysfunction[26,27].

In our patients, the average time of detection of hypothyroidism was 16 months, longer than that reported by other studies[13]. It should be noted that in some cases the diagnosis was made up to 5 years after receiving the I^{131}-MIBG.

Other drugs can block iodine uptake (oral stable iodine), block the binding of iodine to thyroglobulin (methimazole), decrease iodine uptake (levothyroxine), block the sodium/iodide transporter (perchlorate), and some groups have attempted to perform conjugate blockade with the administration of methimazole and levothyroxine, however, the risk of myelotoxicity caused by methimazole may outweigh the benefit[15].

While the use of multiple drugs to block iodine uptake may improve the chance of not developing hypothyroidism (although not by 100%), the monotherapy with only oral stable iodine, may have been a determining factor in the high number of cases detected in the patients studied.

Chemotherapy may be another mechanism that causes thyroid dysfunction in these patients. Specifically, vincristine interferes with the microtubule-microfilament system of the thyrocyte and inhibits thyroglobulin endocytosis by thyroid cells and thyroid hormone secretion, while cisplatin has a direct cytotoxic effect on thyrocytes[28]. In patients with neuroblastoma who were not treated with I^{131}-MIBG doses, whole-body radiotherapy has been reported as a risk factor for hypothyroidism[27].

Although we do not have a thyroid profile before the start of chemotherapy and administration of I^{131}-MIBG, all patients had a normal neonatal screening, including thyroid profile, thus we can be sure that none of them had congenital hypothyroidism and that acquired hypothyroidism was secondary to oncological treatment.

Since thyroid hormones have a primary function for adequate global and neurological development during the first 2 years of extra-uterine life in humans, their dysfunction can result in growth failure and intellectual disability[29].

According to what has been observed in this series, we recommend that every patient with neuroblastoma should have their thyroid profile done at the beginning and on an annual basis, and whenever therapeutic dose of I^{131}-MIBG is administered, thyroid function should be monitored every six months for up to 5 years after the oncological diagnosis, in order to detect alterations early.

It is important to note that in this type of patient, in addition to follow-up for thyroid function, there are

other endocrine disorders such as growth hormone deficiency, hypogonadism, and diabetes, which should be early identified[27,30].

As limitations of the study, we consider that a prospective study is required to better assess the factors involved in the development of hypothyroidism. The sample size is limited, so this should be approached cautiously. Finally, due to its retrospective nature, it was not possible to perform serial measurements of the thyroid profile that would allow a stronger association between risk factors and thyroid dysfunction.

Conclusion

In conclusion, the frequency of hypothyroidism following I^{131}-MIBG administration was 56%. We were unable to identify all factors influencing the development of thyroid dysfunction in children with neuroblastoma, however, inadequate follow-up can have serious consequences, such as neurodevelopmental delay. Therefore, in patients with neuroblastoma, a thyroid profile should be performed every six months and an annual evaluation by a pediatric endocrinologist is warranted during the first 5 years after the oncological diagnosis.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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