

Nasolacrimal duct obstruction as a complication of iodine-131 therapy in patients with thyroid cancer

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Purpose There are few studies evaluating the effect of radioiodine therapy on the lacrimal drainage system. This study reports on symptomatic and asymptomatic nasolacrimal duct obstruction (NLDO) as complications of high-dose radioiodine therapy in these patients.

Methods Eighty-one cases were randomly selected from a population of radioiodine-treated differentiated thyroid carcinoma patients and were enrolled in a historical cohort study. The patients were categorized into four subgroups on the basis of the received cumulative dose of iodine-131 (I-131). In addition, 17 age-matched and sex-matched individuals were selected as the control group. Using dacryoscintigraphy and a clinical datasheet, the patients and controls were evaluated for partial or complete and symptomatic or asymptomatic NLDO. The data on different subgroups of patients were compared with the data of the control group.

Results Twenty-nine out of 162 exposed eyes (18%) and three out of 34 control eyes (9%) had evidence of NLDO on scintigraphic images. Among patients treated with less than 11.1 GBq of I-131 (subgroup A), six out of 78 eyes

(7.7%) had partial or complete NLDO. This was evident in 23 out of 84 eyes (27.4%) among patients treated with 11.1 GBq or more (subgroup B). The frequency of complete NLDO increases significantly when the cumulative dose of radioiodine exceeds 11.1 GBq (2.9% in the control group, 3.8% in subgroup A, and 23.8% in subgroup B; $P=0.006$).

Conclusion NLDO may be considered as a side effect of I-131 therapy, especially with a cumulative dose of 11.1 GBq or more. *Nucl Med Commun* 33:1077–1080 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Radioactive iodine-131 (I-131) was first used for the treatment of differentiated thyroid carcinoma (DTC) in 1941 [1]. Common side effects of I-131 include nausea, vomiting, acute and chronic sialadenitis with xerostomia, lacrimal gland dysfunction, ageusia, and thyroiditis [2–6]. Cytopenia (usually transient) may occur after 6 weeks [7]. Among the late side effects, chronic sialadenitis and xerostomia are more common [4]. Second primary malignancies are worrisome [8]; however, there are reports that do not support a significant increase in the risk of these complications [9,10]. Ocular complications have been reported to occur in 16–23% of patients, including conjunctivitis, xerophthalmia, and epiphora [5,6,11,12]. Epiphora has been introduced as an ocular side effect of I-131 [11,13], which may be more prominent in cumulative doses of more than 5.5 GBq [14]. Although there are few experiences on the association of I-131 and epiphora [11,14], nasolacrimal duct obstruction (NLDO) has not yet been assessed with an objective test in patients treated with I-131.

Dacryoscintigraphy is a rapid, simple, and noninvasive objective method that facilitates definite diagnosis of obstruction and stenosis of the lacrimal drainage system [15]. Using lacrimal duct scintigraphy in this study, we tried to objectively evaluate NLDO as a probable complication of high-dose radioiodine therapy for thyroid cancer.

Methods

Study population

This study was approved by the ethics committee of the Tehran University of Medical Sciences. Between March 2005 and February 2006, 1424 patients were admitted at our institute and were treated with at least 3.7 GBq of I-131. A stratified random sampling of these patients was performed. We divided the patients into four groups on the basis of the cumulative doses of I-131: 3.7–7.3, 7.4–11, 11.1–14.7, and 14.8 GBq or more. Thereafter, the same proportion of patients from each group was selected using a simple random sampling method. These patients were asked to enter the study by contacting them by

telephone. A history of external radiograph therapy to the head and neck, presence of dacryocystitis, congenital NLDO, trauma to the nasolacrimal (NL) apparatus, and surgery or manipulation of the NL apparatus were considered as exclusion criteria. Patients who were determined to be ineligible and those who refused to enter the study were excluded and the next patient record on the random list was selected. A total of 81 patients (Table 1) entered this historical cohort study. A control group consisting of 17 volunteers without any history of epiphora, external radiograph therapy to the head and neck, presence of dacryocystitis, congenital NLDO, trauma to the NL apparatus, and surgery or manipulation of the NL duct were also selected. Informed consent forms were obtained from all the exposed and control cases. A post-hoc analysis was performed, and there were no significant differences in sex and age between different patient subgroups and the control group (P value = 0.515 for sex based on Fisher's exact test and 0.126 for age based on the t -test).

Image acquisition and interpretation

The patients were instructed to wear no eye makeup on the admission day. Each patient was asked to wash his/her face and nasal cavity; this was followed by a 2 min massage of the medial epicanthus. A head support was used to fix the patient's head while he or she was seated in front of a single-head ADAC gamma camera (Argus, Milpitas, California, USA) equipped with a low-energy all-purpose collimator. Technetium-99m sodium pertechnetate (1 MBq) in 10 μ l saline was instilled into the lateral aspect of the lower fornix of each eye using a micropipette. Dacryoscintigraphy was started immediately in dynamic mode on a 64 \times 64 matrix and continued for 12 min. The scans were interpreted by two nuclear medicine physicians. In case of discrepancy, a third physician's opinion was requested. The physicians were unaware of the cumulative dose of radioiodine and clinical status of the studied individuals. The NL drainage was

graded on the basis of dacryoscintigraphy into three categories: the NL apparatus was considered patent (normal) when the activity passed into the nasal cavity within 3 min of instillation; delayed drainage by 12 min was considered as partial obstruction; and no drainage was considered as complete obstruction (Fig. 1).

Statistical analysis

Fisher's exact and the Mann-Whitney U -tests were applied for analyses of categorical and numerical variables, respectively. The Jonckheere-Terpstra test was applied to test for ordered differences between the control group and different patient groups. P values less than or equal to 0.05 were considered significant. A binary logistic regression analysis was used to predict the likelihood of obstruction from independent variables such as sex, last I-131 dose, cumulative I-131 dose, and time interval after the first and last I-131 doses. Risk ratios on 95% confidence intervals were also calculated.

Results

Demographic and clinical baseline data of the patients in different subgroups have been summarized in Table 1. Out of 162 eyes among radioiodine-treated patients 23 (14.2%) showed complete NLDO and six eyes (3.7%) showed partial NLDO. For the control group these values were one eye out of 34 (2.9%) for complete NLDO and two eyes (5.9%) for partial NLDO (subgroup details are shown in Table 2). The proportional frequency of symptomatic NLDO in the patients was 9.8% (16 out of 162 eyes), of which 8.6% (14 out of 162 eyes) were detected as complete NLDO and 1.2% (2 out of 162 eyes) as partial NLDO, whereas there was no symptomatic NLDO in the control group (subgroup details are shown in Table 3). There was significant difference (Jonckheere-Terpstra statistic = 2.774; P = 0.006) in the degree of NL drainage from normal to complete obstruction across the studied subgroups in the order of cumulative doses from 0 GBq

Table 1 Baseline data of the patient subgroups

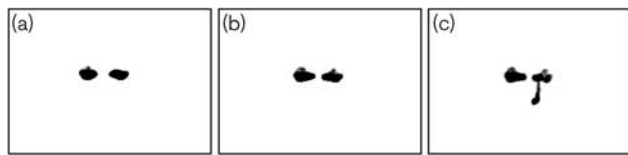
Baseline variables	Patient subgroups				Total N=81
	3.7–7.3 GBq N=21	7.4–11 GBq N=18	11.1–14.7 GBq N=18	\geq 14.8 GBq N=24	
Age					
Mean \pm SD	40.2 \pm 9.9	45.3 \pm 10.8	43.4 \pm 13.7	49.8 \pm 17.3	44.9 \pm 13.7
Sex					
Female/male	18/3	15/3	14/4	18/6	65/16
Cumulative dose of I-131 (GBq)					
Mean \pm SD	4.5 \pm 0.84	8.1 \pm 0.82	12.1 \pm 0.98	21.2 \pm 6.4	11.9 \pm 7.5
Median	4.6	7.4	12	21.2	11.1
The last dose of I-131 (GBq)					
Mean \pm SD	4.5 \pm 0.84	4.5 \pm 1.1	5.8 \pm 0.81	6.5 \pm 0.86	5.4 \pm 1.2
Median	4.6	3.7	5.5	6.5	5.5
Period after the first dose of I-131 (months)					
Mean \pm SD	20.7 \pm 17.7	41.3 \pm 43.4	44.9 \pm 31.9	49.2 \pm 27.1	39 \pm 3.2
Median (range)	17 (10–93)	31 (8–191)	37 (12–45)	38 (13–127)	31 (8–191)
Period after the last dose of I-131 (months)					
Mean	20.7 \pm 17.7	14.6 \pm 12	11.9 \pm 5.2	8.4 \pm 6.5	11
Median (range)	17 (10–93)	12 (2–51)	11.5 (4–22)	7 (2–34)	11 (2–93)

I-131, iodine-131.

(control group) to at least 14.8 GBq (Table 2). On the basis of the data in this table, the frequency of complete NLDO in the subgroups with cumulative doses less than 11.1 GBq (3.8%, three out of 78) did not increase significantly compared with the control group (2.9%), whereas this frequency was markedly increased in patients treated with a cumulative I-131 dose of at least 11.1 GBq (23.8%, 20 out of 84 eyes).

As noted in Table 3, among the patients treated with less than 11.1 GBq of I-131, five out of 78 eyes (6.4%) had asymptomatic NLDO and one (1.3%) had symptomatic obstruction. These values for patients treated with more than 11.1 GBq were eight (9.5%) and 15 (17.8%) out of 84 eyes, respectively ($P = 0.001$).

Fig. 1



Selected images from a dacryoscintigraphy. (a) Immediately after radiotracer instillation, uniform radiotracer distribution in the lacrimal apparatus is noted bilaterally. (b) Five minutes later, there is no entrance of the tracer into the lacrimal sac on either side. (c) Nine minutes after instillation, radiotracer entrance to the lacrimal sac and subsequently to the nasolacrimal duct is noted on the left side, whereas the obstruction persisted on the right side. The scan was interpreted as complete obstruction on the right side and partial obstruction in the proximal nasolacrimal duct on the left side.

In multivariate analysis, the effect of independent variables, that is, sex, the first and last I-131 doses, and the periods after the first and last doses and the cumulative dose, on the occurrence of NLDO was assessed by the binary logistic regression test. The cumulative dose of more than 11.1 GBq was the only significant predictor of NLDO in our patients [odds ratio = 3.922 ($P = 0.029$) for the right side and odds ratio = 5.78 ($P = 0.031$) for the left side].

Discussion

Morgenstern *et al.* [16] showed that NIS protein is expressed in NL duct epithelial cells. To the best of our knowledge, the present study is the first investigation on NL duct function using a physiological objective test, that is, radionuclide dacryoscintigraphy, in I-131-treated DTC patients for an analytic comparison between the effects of different cumulative doses.

In a study by Burns *et al.* [11], the incidence of documented NLDO was 3.4% and the overall incidence (documented and suspicious) was 4.6%. In this study, only symptomatic patients were evaluated and no objective diagnostic test for the evaluation of NL drainage was conducted to confirm NLDO before intervention. In our institution, a random sample from the population of all radioiodine-treated patients irrespective of their clinical symptoms was used to study the diagnosis of NLDO by dacryoscintigraphy before any intervention. In contrast, the patients were stratified on the basis of the radioiodine cumulative dose to estimate the prevalence of NLDO in different subgroups and to find a possible relationship between the dose and NLDO. About 18%

Table 2 The frequency of partial and complete nasolacrimal duct obstruction in different subgroups of iodine-131-treated patients versus the control group

Scintigraphic findings	Control group 34 eyes	Patient subgroups				Significance
		3.7–7.3 GBq 42 eyes	7.4–11 GBq 36 eyes	11.1–14.7 GBq 36 eyes	≥ 14.8 GBq 48 eyes	
Normal	31 (91.2%)	40 (95.2%)	32 (88.9%)	24 (66.7%)	37 (77.1%)	0.006*
Partial obstruction	2 (5.9%)	1 (2.4%)	2 (5.6%)	2 (5.6%)	1 (2.1%)	
Complete obstruction	1 (2.9%)	1 (2.4%)	2 (5.6%)	10 (27.8%)	10 (20.8%)	

*Significant with the Jonckheere–Terpstra test.

Table 3 The frequency of symptomatic and asymptomatic nasolacrimal duct obstruction in different subgroups of iodine-131-treated patients versus the control group

	Control group 34 eyes	Patient subgroups				P*
		3.7–7.3 GBq 42 eyes	7.4–11 GBq 36 eyes	11.1–14.7 GBq 36 eyes	≥ 14.8 GBq 48 eyes	
Normal	31 (91.2%)	40 (95.2%)	32 (88.9%)	24 (66.7%)	37 (77.1%)	0.001
Asymptomatic NLDO	3 (8.8%)	1 (2.4%)	4 (11.1%)	7 (19.4%)	1 (2.1%)	
Symptomatic NLDO	0	1 (2.4%)	0	5 (13.9%)	10 (20.8%)	

NLDO, nasolacrimal duct obstruction.

*The Jonckheere–Terpstra test and Pearson’s χ^2 -test.

of our patients showed partial or complete NLDO on dacryoscintigraphy (29 out of 162 eyes), whereas the frequency of NLDO in the control group was less than 9%. The proportional frequency of patients with symptomatic complete NLDO in our study was 8.6%, all of whom were in the radioiodine-exposed group.

This difference in reported incidence may be because in Burns' study only symptomatic patients were included, whereas in our study both symptomatic and asymptomatic patients were evaluated objectively by dacryoscintigraphy; besides, some partial NLDO (less symptomatic ones) could have been missed. In contrast, a higher incidence of symptomatic NLDO is anticipated in our study as many patients had been treated with higher doses of radioiodine.

According to our data, the frequency of complete NLDO rises slightly in cumulative doses of less than 11.1 GBq, whereas it increased significantly with a cumulative dose of 11.1 GBq or more (mean = 15.9 GBq); however, partial obstruction did not increase significantly. Thus, complete NLDO could be considered as a side effect of high-dose I-131 therapy with a threshold of 11.1–14.8 GBq. This was also confirmed in multivariate analysis, whereby the cumulative dose of I-131 was shown to be the only predictor of NLDO after adjusting for baseline variables such as sex, dose, and elapsed time from the first and last I-131 administrations.

Conclusion

This study confirms an association between high doses (≥ 11.1 GBq) of I-131 therapy and NLDO in DTC patients.

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Conflicts of interest

There are no conflicts of interest.

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