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Pituitary Tumors Following Fallout Radiation Exposure

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• **Two pituitary tumors were diagnosed in a small population of Marshallese accidentally exposed to radioactive fallout in 1954.** (*JAMA* 1984;252:664-666)

IN 1954, the populations of two atolls in the Marshall Islands were accidentally exposed to radioactive fallout from a test detonation of a thermonuclear bomb. The acute and delayed effects of their radiation exposure have been the subject of numerous publications (an extensive listing can be found in reference 1). In brief, the average total-body external gamma radiation received on the islands of Rongelap (64 persons), Ailingnae (18 persons), and Utirik (157 persons) has been calculated to be 190, 110, and 11 rad, respectively.[2] All survived the initial effects of hematopoietic suppression and skin burns. Internalization of radionuclides also occurred, including radioactive iodines. Long-term follow-up has revealed, as a consequence, a high incidence of thyroid neoplasia and hypofunction, especially among those persons who had been on Rongelap and Ailingnae.[3,4] We now report the newest endocrinologic finding in the exposed population, that being two cases of pituitary tumor, and address the possible relation of the tumors to radiation exposure and thyroid disease.

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Report of Cases

CASE 1.—A Rongelap woman was 20 years old when exposed to radioactive fallout. In addition to receiving an estimated total-body absorbed dose of 190 rad of external gamma radiation, an estimated 1,100 rad was absorbed by her thyroid gland due to intake of radioactive iodines and telluriums.[2] Thyroxin supplementation was begun at age 32 years following the discovery of thyroid nodules in other exposed Rongelapese. Three years later, however, a total thyroidectomy was performed for papillary carcinoma. Roentgenograms of the skull, taken as part of a routine follow-up examination seven years later (1976), unexpectedly revealed erosion of the anterior floor of the sella turcica and a mass extending into the sphenoid sinus (Fig 1). She had no symptoms suggesting a pituitary lesion, and visual field examination results were normal. She had borne 14 children by age 35 years and continued to have normal menstrual cycles. Oral contraceptives were never used. Evaluation at the Clinical Center of the National Institutes of Health (under the care of Jacob Robbins, MD) confirmed the roentgenographic findings, and computed tomography (CT) revealed no suprasellar extension of the tumor. Thyroid function tests performed in the years prior to diagnosis are presented in Table 1. Endocrinologic studies indicated normal levels of serum follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, morning cortisol, total thyroxine, free thyroxine, and triiodothyronine. The diagnosis of a nonfunctioning pituitary adenoma was made, and therapeutic irradiation was administered. During the six-year follow-up, menstrual function and results of visual field examinations and endocrinologic studies have remained normal. (Data from this patient are also presented in reference 1.)

CASE 2.—A 29-year-old woman was younger than 1 year at the time of her radiation exposure on Utirik. In contrast to most of the other exposed inhabitants, she left the fallout area within 24 hours of its onset and never returned to the atoll. External whole-body and thyroid radiation absorbed doses were estimated at 11 and 660 rad, respectively.[2] Menarche was at age 13 years, but within a few years she became amenorrheic. Although subsequently married, she had no pregnancies. Oral contraceptives were not used. Results of annual physical examinations by Brookhaven National Laboratory physicians were routinely normal, although the uterus was thought to be somewhat small. A history of galactorrhea was obtained in 1977. Her thyroid-stimulating hormone levels at ages 18, 24, and 25 years were normal (Table 1). Evaluation for secondary amenorrhea at age 26 years revealed a serum prolactin level of 480 ng/mL. She was subsequently admitted to the Clinical Center of the National Institutes of Health (under the care of D. Lynn Loriaux, MD), where CT of the sella

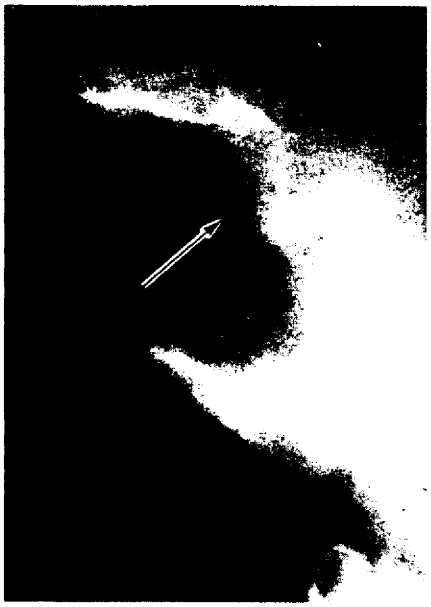

Fig 1.—Tomogram of case 1, with arrow indicating erosion of sella turcica and mass extending into sphenoid sinus.

Table 1.—Serial Thyroid-Stimulating Hormone* (TSH) Levels in Two Patients With Pituitary Tumors

Year	Case 1*	Case 2
1965	2.2	. . .
1967	1.0	. . .
1969	1.7	. . .
1972	110	<2.5
1973	. . .	. . .
1974	1.0	. . .
1975	5.9	. . .
1976	115‡	. . .
1978	1.8	1.7
1979	. . .	0.3
1981	<2.5	<2.5‡

*Normal values are less than 5 μU/mL.

†Case 1 had a total thyroidectomy in 1969 for papillary carcinoma, and the elevated TSH levels in 1972 and 1976 were obtained when thyroxine therapy was discontinued prior to iodine 131 scanning.

‡Year pituitary tumor was diagnosed.

turcica suggested the presence of a 1.2-cm pituitary adenoma with no suprasellar extension. Preoperative endocrine evaluation showed the following to be normal: one-hour adrenocorticotropic hormone (ACTH) stimulation test results, growth hormone and cortisol responses to an insulin tolerance test, free and total serum thyroxine levels, and thyroid-stimulating hormone values. Subsequently, transsphenoidal removal of an intrasellar adenoma was performed. A soft-tissue tumor that contained many small cystic foci was found. Immunofluorescent staining of the tumor was positive for prolactin (Fig 2). Two weeks postoperatively, thyroid functions and results of a one-hour ACTH stimulation test were normal, and serum prolactin values had decreased to 68 ng/mL. She remains amenorrheic one year postoperatively.

Fig 2.—With immunofluorescent staining, dark cytoplasmic reaction product, indicated by arrows, can be seen localizing prolactin in cells of pituitary adenoma of case 2. Prolactin-secreting cells have round to oval nuclei and distinct nucleoli (×800).

Prolactin assays performed on stored frozen sera obtained from her annual examinations have revealed prolactin elevations ranging from 209 to 609 ng/mL as far back as 1975, at which time she was 21 years of age.

Results

Analysis of Epidemiologic Data.—Incidence figures for pituitary tumors in the United States are not available from the National Tumor Registry or the National Cancer Institute's Biometric Division because they are not considered malignant. Several studies suggest an incidence approaching one in 100,000 persons per year among those younger than 45 years, distributed equally between the sexes.[5] However, these retrospective studies occurred before modern methods of pituitary tumor diagnosis were available.

Data from the Olmsted County, Minnesota, epidemiologic study of pituitary tumors[6] and the 1970 and 1980 census information for that county provide information that may be used (as a referent) in comparison with the Marshallese data. In Olmsted County, the incidence rate of pituitary tumors among women aged 15 to 44 years during the years 1971 through 1977 was 11 cases per 163,096 person years. For radiation-exposed Marshallese women in the same age group, the rate is two cases per 2,176 person years. The incidence rate for the Marshallese women is 13.6 times higher than that for the Olmsted County women; that is, the relative risk, as estimated by the incidence density ratio, is 13.6.[7] If the propensity for pituitary tumors developing were the same for each population studied, then the relative risk should be near unity, allowing for random variation. An exact (binomial) test, which is appropriate where numerators are small, indicates that the relative risk is significantly greater than unity at the α=0.01 level.

Table 2.—Statistical Analysis of Relative Risk of Pituitary Tumor in Radiation-Exposed Marshallese

Population	Incidence	Person Years
Women, 15-44 yr*		
Marshall Islands	2	2,176
Olmsted County	11	163,096
Total population, 45 yr†		
Marshall Islands	2	4,252
Olmsted County	12	454,472

*Relative risk, 13.6; 95% confidence interval, 4, 42; *P* value, .01.

†Relative risk, 17.8; 95% confidence interval, 6, 53; *P* value, .001.

Table 2 provides relative risks, exact *P* values, and approximate confidence intervals for women aged between 15 and 44 years and for men and women combined who are younger than 45 years of age, using Olmsted County as the referent population.

No allowance is made in the incidence data for any latent period in tumor induction because there are no published data on this point. The two pituitary tumors, however, were clearly present 21 and 22 years after radiation exposure. The statistical analyses also ignore the fact that the Marshallese people exposed to radioactive fallout have been followed up more closely than any large control population. Finally, the baseline frequency of pituitary tumors in the Marshall Islands is unknown. While no cases have been diagnosed in a comparison population of unexposed Marshallese, the number of person-years of observation is small (698 person-years for women aged 15 to 44 years; 1,527 person-years for the total population younger than 45 years). This does not permit a meaningful statistical analysis of pituitary tumor incidence in the Marshall Islands.

Nevertheless, the absence of cases in the unexposed group does tend to support the results of the statistical analysis using data from Olmsted County.

Prolactin Survey.—Serum prolactin levels were determined on nonfasting blood specimens obtained in 1982 from 174 of the 178 remaining persons with a history of radiation exposure in 1954. (Prolactin radioimmunoassays were performed in the laboratory of P. R. Larsen, MD, Brigham and Women's Hospital, Boston.) The mean prolactin level plus or minus 2 SDs was 6.9 ± 11.8 ng/mL for men and, after exclusion of values obtained during pregnancy or lactation, 9.0 ± 12.8 ng/mL for women. Seven persons had levels exceeding 2 SDs of the mean; six were not elevated when rechecked on a subsequent sample. One persistent and unexplained elevation (serum prolactin level, 42 ng/mL) was discovered in an asymptomatic but childless 82-year-old woman. Skull roentgenograms showed a normal sella turcica. Because (1) there was no evidence of a mass lesion (including the findings of an ophthalmologist's examination), (2) prolactin elevation was minimal, and (3) the patient was of an advanced age, further evaluation was not carried out. It is not certain, therefore, that she has a pituitary tumor.

Comment

Subclinical tumors of the pituitary gland are common, being found in up to 27% of consecutive necropsies.[8,9] Nevertheless, clinically diagnosed tumors are infrequent, although CT and newer assays for pituitary hormones, especially prolactin, may be increasing the frequency of the diagnosis.[10] The reason for the apparent increase in relative risk of clinically significant pituitary tumors in radiation-exposed Marshallese is unknown. Sixteen percent of the more heavily exposed Rongelap-Ailingnae population have had subclinial thyroid hypofunction develop.[4] The possibility of an endocrine "domino" effect is suggested by human and animal data indicating that dysfunction and hyperplasia-adenoma formation of pituitary cells can result from thyroid hypofunction.[11-13] In addition, hypothyroidism is sometimes associated with hyperprolactinemia or galactorrhea or both.[14] Hypothyroidism in general, however, has not been associated with an increase in pituitary tumors in humans. Furthermore, our two patients were clinically and biochemically euthyroid when tested in the years preceding their diagnoses (see Table 1 for exceptions), although subclinical thyroid hypofunction in the early years after fallout exposure cannot be excluded because sensitive thyroid-stimulating hormone assays were unavailable at that time.

External gamma irradiation of experimental animals has produced pituitary tumors.[15] There have been no prior reports implicating the same mechanism in humans. No increase in incidence of pituitary tumors has been noted among survivors of the atomic bombings in Japan or among children who received cranial radiation, although the incidence of other intracranial tumors is elevated.[16-19] Internally deposited, short-lived radioisotopes of iodine are considered the cause of the high incidence of thyroid neoplasia in the exposed Marshallese,[3] but there is no equivalent concentration of fallout nuclides that might lead to a high absorbed dose in the human pituitary. Nevertheless, pituitary tumors have been found in offspring of pregnant mice intravenously injected with strontium 90 and in rats given intraperitoneal injections of strontium 90 or cerium 144,[20,21] and orally administered yttrium 90 concentrates in the pituitary of guinea pigs.[22] While the relevance to humans of such animal research is clearly important, differences in species responses and circumstances of exposure do not permit the inference of a causal association between the radiation received by the subjects of this report and subsequent pituitary neoplasia.

In conclusion, the development of two pituitary tumors in this relatively small population may be evidence that certain types of radiation can induce pituitary neoplasia in humans. The link is not a strong one, however, being a statistical phenomenon unassociated with a known biologic basis.

Jacob Robbins, MD, and D. Lynn Loriaux, MD, gave permission to use clinical data on their patients, and Paul E. McKeever, MD, provided the photograph and histologic interpretation of the prolactinoma in case 2. Geraldine Callister provided secretarial services, and William A. Scott and Peter M. Heotis provided the administrative management of patients and data. Claire J. Shellabarger, PhD, reviewed the manuscript.

References

1. Conard RA, Paglia DE, Larsen PR, et al: *Review of Medical Findings in a Marshallese Population 26 Years After Accidental Exposure to Radioactive Fallout*, Brookhaven National Laboratory report 51261. Upton, NY, Brookhaven National Laboratory, 1980.

2. Lessard E, Miltonberger R, Cohn S, et al: Exposure to fallout: The radiation dose experience at Rongelap and Utirik atolls, Brookhaven National Laboratory abstract 32510. Presented at the Seventh International Congress of Radiation Research, Amsterdam, July 3-8, 1983.

3. Conard RA, Rall JE, Sutow WW: Thyroid nodules as a late sequela of radioactive fallout. *N Engl J Med* 1966;274:1392-1399.

4. Larsen PR, Conard RA, Knudsen KD, et al: Thyroid hypofunction after exposure to fallout from a hydrogen bomb explosion. *JAMA* 1982; 247:1571-1575.

5. Gold EB: Epidemiology of pituitary adenomas. *Epidemiol Rev* 1981;3:163-183.

6. Annegers JF, Coulam CB, Abboud CF, et al: Pituitary adenoma in Olmsted County, Minnesota, 1935-1977. *Mayo Clin Proc* 1978;53:641-643.

7. Miettinen OS: Estimability and estimation in case-referent studies. *Am J Epidemiol* 1976; 103:226-235.

8. Costello RT: Subclinical adenoma of the pituitary gland. *Am J Pathol* 1936;12:205-215.

9. Burrow GN, Wortzman G, Rewcastle NB, et al: Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. *N Engl J Med* 1981;304:156-158.

10. Collins WF: Adenomas of the pituitary gland—an epidemic? *Surg Clin North Am* 1980; 60:1201-1206.

11. Russfield AB: Histology of the human hypophysis in thyroid disease—hypothyroidism, hyperthyroidism, and cancer. *J Clin Endocrinol Metab* 1955;15:1393-1408.

12. Bigos ST, Ridgway EC, Kourides IA, et al: Spectrum of pituitary alterations with mild and severe thyroid impairment. *J Clin Endocrinol Metab* 1978;46:317-325.

13. Furth J, Moy P, Hershman JM, et al: Thyrotropic tumor syndrome. *Arch Pathol* 1973; 96:217-226.

14. Contreras P, Generini G, Michelsen H, et al: Hyperprolactinemia and galactorrhea: Spontaneous versus iatrogenic hypothyroidism. *J Clin Endocrinol Metab* 1981;53:1036-1039.

15. Furth J, Haran-Ghera N, Curtis HJ, et al: Studies on the pathogenesis of neoplasms by ionizing radiation. *Cancer Res* 1959;19:550-556.

16. Kato H, Schull WJ: Studies of the mortality of A-bomb survivors: 7. Mortality, 1950-1978: Part 1. Cancer mortality. *Rad Res* 1982;90:395-432.

17. Seyama S, Ishimaru T, Iijima S, et al: *Primary Intracranial Tumors Among Atomic Bomb Survivors and Controls, Hiroshima and Nagasaki, 1961-1975*, report TR 15-79. Radiation Effects Research Foundation, 1979.

18. Modan B, Baidatz D, Mart H, et al: Radiation-induced head and neck tumors. *Lancet* 1974;1:277-279.

19. Shore RE, Albert RE, Pasternack BS: Follow-up study of patients treated by X-ray epilation for tinea capitis. *Arch Environ Health* 1976;31:17-24.

20. Schmahl W, Kollmer WE: Radiation-induced meningeal and pituitary tumors in the rat after prenatal application of strontium-90. *J Cancer Res Clin Oncol* 1981;100:13-18.

21. Moskalev YI, Streltsova VN, Buldakov LA: Late effects of radionuclide damage, in Mays CW, Jee WSS, Lloyd RD, et al (eds): *Delayed Effects of Bone-seeking Radionuclides*. Salt Lake City, University of Utah Press, 1969, pp 489-509.

22. Graul EH, Hundeshagen H: ^{90}Y-Organverteilungstudien unter besonderer Berucksichtigung des autoradiographischen und papierlektrophoretischen Nachweisverfahrens. *Strahlentherapie* 1958;106:405-417.

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