



## Multiple Endocrine Neoplasia Type 1 Parathyroid Adenoma Development over Time

Gerard M. Doherty, M.D.,<sup>1</sup> Terry C. Lairmore, M.D.,<sup>2</sup> Mary K. DeBenedetti, R.N.<sup>2</sup>

<sup>1</sup>Department of Surgery, University of Michigan, 2920 Taubman Center, 1500 East Medical Center Drive, Ann Arbor, Michigan, 48109-0331 USA

<sup>2</sup>Department of Surgery, Washington University, 660 South Euclid Avenue, St. Louis, Missouri 63110, USA

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**Abstract.** Multiple gland parathyroid disease is one of the hallmarks of multiple endocrine neoplasia (MEN) type 1. Often mislabeled *parathyroid hyperplasia*, the process is actually the development of multiple adenomas. Some clinicians have reported results of selective parathyroidectomy in this group, removing only grossly enlarged glands. We argue that all the glands are at risk and should be addressed at any planned parathyroid intervention. Our hypothesis is that, given sufficient time, patients would all develop adenomas in each of the parathyroid glands. Our available data to address this issue are the parathyroidectomy results from a single institution series. Patients who had initial parathyroid exploration for hyperparathyroidism in the setting of MEN-1 were reviewed. This study includes those patients who had the weights of the resected glands documented; 23 men and 21 women met the criteria. The total weight of the parathyroid glands did not vary with the age of the patient at operation. However, the number of normal glands identified did vary significantly with age ( $p < 0.02$ ), with older patients being less likely to have any normal parathyroid glands. Although total parathyroid weight may correlate with development of hypercalcemia and indications for operation, the involvement of multiple parathyroid glands in MEN-1 is a function of time, as independent events in each gland must occur. Given time, MEN-1 patients all develop multiple gland disease, and this reality must be used in planning operative management for patients with this syndrome.

Multiple gland parathyroid disease is the most frequently expressed of the classic features of multiple endocrine neoplasia type 1 (MEN-1), and it is often asymmetric [1]. Although some authors in the past have proposed strategies that address only glands that are grossly enlarged at operation [2], most now agree that any operation for hyperparathyroidism in these patients should address all of the parathyroid glands, because they all may eventually become abnormally enlarged and cause hypercalcemia. The generally accepted operative options include subtotal parathyroidectomy and total parathyroidectomy with a parathyroid autograft to address the multiple gland disease [3–6].

The nature of multiple-gland disease (MGD) in MEN-1 is different from other frequently treated MGD situations, such as the

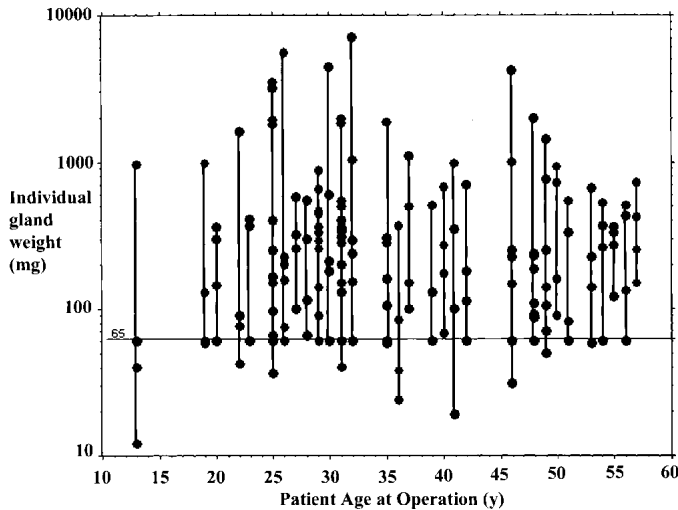
parathyroid hyperplasia leading to renal osteodystrophy. In the past some investigators have proposed that there is a circulating factor in MEN-1 that causes parathyroid hyperplasia [7]. However, other evidence regarding the clonality of parathyroid adenomas has indicated that this is a neoplastic process rather than a hyperplastic process [8, 9]. These data imply that the germline mutation in MEN-1 allows the development of multiple parathyroid adenomas, a process that requires discrete second events in each parathyroid gland. We hypothesized that the probability of the “second hit” occurring in any individual parathyroid gland would increase with time, and thus the likelihood of having any normal parathyroid glands would decrease with age. The chance of having a second hit occur in each of the parathyroid glands simultaneously would also seem to be low. The difference in the time at which these events occur seems likely to cause the development of asymmetrical gland enlargement, as the multiple independent parathyroid adenomas each begin development at different times. Here we report the parathyroid gland weights for 44 MEN-1 patients who underwent their initial parathyroid operation at Washington University in St. Louis, MO, USA, and who had the gland weights documented, to evaluate our hypothesis.

### Materials and Methods

MEN-1 kindred members treated at Washington University are followed through the Multiple Endocrine Neoplasia Program, and their clinical data are maintained in a prospective database as a part of an IRB-approved research program. Patients who had their initial parathyroidectomy at Washington University were extracted from the database, and those who had parathyroid gland weight documented were included in this study. Each patient had the diagnosis of hyperparathyroidism confirmed by simultaneous elevations of serum levels of calcium and parathyroid hormone. Operative exploration was carried out via a standard approach designed to identify all parathyroid tissue within the neck and anterior mediastinum. All patients had a transcervical thymectomy as a part of the exploration, to remove all accessible thymus tissue, and any parathyroid tissue contained within the thymus. Patients had either total parathyroidectomy with autograft, or subtotal parathyroidec-

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Correspondence to: Gerard M. Doherty, M.D., e-mail: gerardd@umich.edu



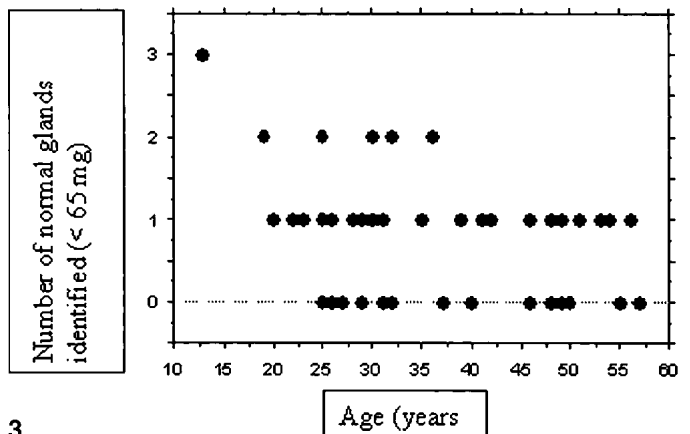
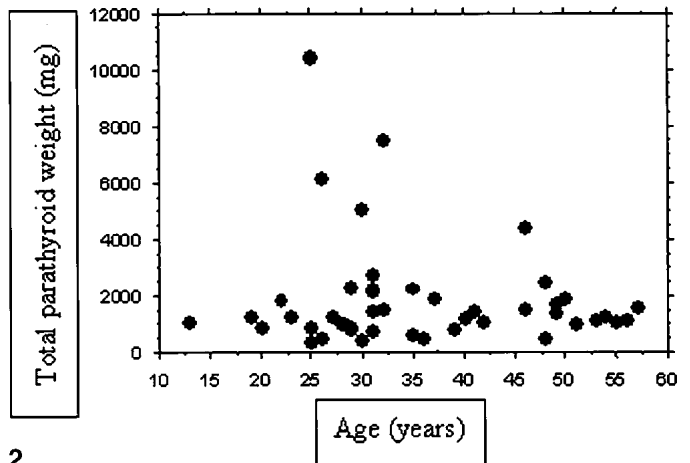
**Fig. 1.** Parathyroid weights versus patient age. The weights of the individual parathyroid glands are plotted in log scale versus the age of the patient at the time of operation. The upper limit of the weight of normal glands is designated as 65 mg. The parathyroid glands from an individual patient are connected by a solid line; however, in all cases where there is more than one patient for a given age, there is overlap of the connecting lines.

tomy, as selected according to surgeon and patient preference. For patients who had subtotal parathyroidectomy, 60–100 mg of the most normal-appearing gland was preserved on its native blood supply prior to removing the remaining glands. For those patients who had total parathyroidectomy and autograft, 60–100 mg of the most normal-appearing gland were autografted, generally into the brachioradialis muscle of the non-dominant forearm. Gland weights were determined as wet-weight in the operating room immediately upon excision of the gland, performed sterilely on a digital scale. Age, total parathyroid gland weight, individual gland weights, and number of normal glands (< 65 mg) were correlated and trends evaluated by regression analysis with significance defined as  $p < 0.05$ .

**Results**

Twenty-three men and 21 women, ranging in age from 13 to 57 years met the criteria for inclusion. The individual gland weights for each patient are given in Figure 1. In this series, 39 of 44 patients had four glands identified at these initial operations. The remaining five patients each had three glands identified. Although some glands were identified within the superior portions of the thymus, all glands were located in typical locations for parathyroid glands. There were no patients with supernumerary glands identified, either within the removed thymus or elsewhere. Except for deliberately preserved parathyroid remnants in the patients who had subtotal parathyroidectomy, every effort was made to remove all of each patient’s parathyroid tissue.

Patients had great variability in the size of their individual parathyroid glands, confirming the asymmetry of involvement. The total weight of the parathyroid glands at operation (sum of the weights of the individual glands) is depicted in Figure 2. The total weight did not vary with the age of the patient at operation. However, the number of normal glands identified did vary significantly with age



**2**

**3**

**Fig. 2.** Total parathyroid weight at the time of operation versus patient age. Each dot represents the summed weights of the parathyroid glands of an individual patient. There was no correlation between the age of the patient at operation and the weight of the parathyroid glands.

**Fig. 3.** Number of normal parathyroid glands versus patient age. Each dot represents the number of normal parathyroid glands (weight < 65 mg) identified at operation. There was a negative correlation between the number of normal glands and age ( $p < 0.02$ ).

(regression analysis,  $p < 0.02$ ), with older patients being less likely to have any normal parathyroid glands (Fig. 3).

**Discussion**

The germline abnormality in MEN-1 is present in each cell of the body; however, disabling changes in the normal copy of *MEN1* that occur in the endocrine pancreas, pituitary, and parathyroid glands (as well as other less common sites) cause the development of multiple adenomas. The nature of the “second hits” leading to parathyroid adenomas dictates that not every parathyroid gland is affected identically or simultaneously, thus leading to the marked asymmetry that has been observed by many surgeons [1]. While total parathyroid weight may correlate with development of hypercalcemia and indications for operation, the parallel involvement of multiple parathyroid glands in MEN-1 is a function of time, as independent events in each gland must occur.

The important findings in this series include confirmation of the asymmetry of the parathyroid adenomas in MEN-1, and demon-

stration of the relationship between age and the likelihood of identifying any normal parathyroid glands. The asymmetry of the parathyroid glands in MEN-1 has been commented on by others, and it has been studied in a similar fashion, using parathyroid volume, by the United States National Institutes of Health (NIH) group [1]. The asymmetry itself did not vary with patient age (Fig. 1), as patients at all ages had glands of varying sizes, a finding similar to those in the NIH study. These data fit with the observations of many surgeons, and this is the observation that led some in the past to propose more limited operative resection for MEN-1 parathyroid disease. Interestingly, in spite of the progression in the number of abnormal glands with age, the total weight of the parathyroid glands did not change significantly with age (Fig. 2). Finally, the likelihood of involvement of each of the parathyroid glands increased with increasing patient age (Fig. 3). This fits well with the hypothesis that independent second hits are necessary for the development of each parathyroid adenoma. The chance of this event having occurred in any one parathyroid gland in any patient should increase with age, and it appears to, according to these data.

The asymmetry of parathyroid gland involvement in MEN-1 led some clinicians to suggest a selective approach to parathyroidectomy, removing only the glands observed to be enlarged at the time of operation [2]. Biologically and clinically, this has not seemed a rational strategy to us. Our working hypothesis of MEN-1 is that, given time, MEN-1 patients all develop multiple gland disease, and this reality must be used in planning operative management of patients with this syndrome. This study demonstrates the data behind that approach, and confirms our understanding of the pathophysiology of MEN-1 parathyroid disease. As age increases, the number of normal parathyroid glands decreases. Thus, in our opinion, and given the potential morbidity of secondary operations in the neck, any operation to address the parathyroid disease in MEN-1 should address all of the parathyroid glands, whether they appear normal or abnormal at the time of the operation. In addition, as a part of that strategy, we advocate removing the cervically accessible thymus at the time of initial operation, to try to remove all sites of parathyroid tissue, as well as to prevent the potential future development of malignant thymoma as a component of MEN-1.

The two operative strategies that are widely used (total parathyroidectomy with autograft, and subtotal parathyroidectomy) each have their weaknesses and failures [4, 10–12]. Neither offers a permanent, reliable solution for the disease. The goal of each operation is to remove most of the parathyroid tissue, and to leave a smaller fragment of functional tissue in a single, defined location. Each operation recognizes the facts that (1) it is better to have a smaller amount of abnormal parathyroid tissue than to have none at all and (2) it is easier to address the recurrent disease if all of the abnormal tissue is left in one place. Each of these operations can fail if not all of the abnormal tissue is addressed at the initial operation, leaving for instance, an abnormal gland that is unidentified in the neck or thymus, or if the deliberately preserved tissue (on its native blood supply or as an autograft) fails to function adequately. Each approach is also expected to “fail” at a later date, as the parathyroid remnant (either in the neck or at the autograft site) can grow, causing the hypercalcemia and hyperparathyroidism to recur [10]. The optimal solution to this disease has not yet been devised, but any potential intervention must address all of the parathyroid glands to be durably successful.

**Résumé.** La maladie multiglandulaire est une des caractéristiques du syndrome MEN-1. Souvent étiquetée à tort «hyperplasie» de la parathyroïde, il s'agit en fait d'un stade de développement des adénomes multiples. Certains cliniciens ont rapporté des résultats de la parathyroïdectomie sélective chez ce groupe de patients, enlevant seulement les glandes augmentées de volume macroscopiquement. Nous pensons que toutes les glandes sont à risque et peuvent faire l'objet d'une exérèse au cours d'une intervention sur la parathyroïde. Notre hypothèse est qu'au fil du temps, les patients auraient tous développé un adénome de chaque parathyroïde. Nous avons adressé cette hypothèse basée sur nos propres données mono-institutionnelles. Les dossiers des patients ayant eu une exploration initiale de la parathyroïde pour hyperparathyroïdisme dans le cadre d'un MEN-1 ont été passés en revue. Cette étude a inclus les patients pour lesquels on a disposé du poids des glandes réséquées. Ont rempli les critères d'inclusion, 23 hommes et 21 femmes. Le poids total des glandes parathyroïdes ne variaient pas avec l'âge au moment de l'intervention. Cependant, le nombre de glandes normales identifiées était proportionnel à l'âge ( $p < 0.02$ ), avec les patients les plus âgés les moins susceptibles d'avoir des glandes normales. Alors que le poids total des parathyroïdes peut corrélérer avec le développement de l'hypercalcémie et les indications pour intervention, la multiplicité des glandes intéressées par le processus dans le syndrome MEN-1 n'est qu'une question de temps, dépendant d'un événement spécifique dans chaque glande. Après un délai suffisamment long, les patients MEN-1 développent tous la maladie multiple et cet état de connaissances doit intervenir dans la décision opératoire chez les patients porteurs de ce syndrome.

**Resumen.** La enfermedad paratiroidea pluriglandular es una de las características del síndrome de neoplasia endocrina múltiple (MEN-1). Con frecuencia es erróneamente designada como hiperplasia paratiroidea, cuando en realidad el proceso es el desarrollo de adenomas múltiples. Algunos autores han informado los resultados de paratiroidectomía selectiva, o sea la resección de sólo las glándulas macroscópicamente hipertróficas en este grupo de pacientes. Nosotros creemos que todas las glándulas se hallan en riesgo y que deben ser consideradas al planear una intervención paratiroidea, bajo la hipótesis de que transcurrido un tiempo suficiente, todos los pacientes desarrollarán adenomas en cada una de las glándulas paratiroideas. Los datos pertinentes de que disponemos ahora provienen de los resultados de una serie de paratiroidectomías realizadas en una sola institución. Se revisaron las historias de los pacientes que tuvieron una exploración paratiroidea inicial en el contexto de un MEN-1. El estudio incluyó aquellos pacientes en que aparecía documentado el peso de las glándulas resecaadas. 23 hombres y 21 mujeres cumplieron los criterios. El peso total de las glándulas paratiroideas no varió con la edad del paciente en el momento de la operación. Sin embargo, el número de glándulas normales identificadas sí varió en forma significativa con la edad ( $p < 0.02$ ), siendo los pacientes mayores quienes con menor frecuencia presentaron alguna paratiroides normal. En tanto que el peso paratiroideo total puede correlacionarse con el desarrollo de hipercalcemia y las indicaciones para operación, la afectación de múltiples glándulas paratiroides en el MEN-1 es una función del tiempo, en la medida que eventos independientes ocurren en cada glándula. Dado un tiempo suficiente, todos los pacientes con MEN-1 desarrollan enfermedad multiglandular, y tal realidad debe ser tenida en cuenta en la planeación del manejo operatorio de pacientes con este síndrome.

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