# Pediatric Head and Neck Manifestations of Multiple Endocrine Neoplasia Syndrome

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## Background

Multiple endocrine neoplasia (MEN) syndromes are a group of autosomal dominant hereditary cancer syndromes associated with pediatric head and neck endocrine neoplasms, both benign and malignant.[1,2]

MEN1 is due to mutations in the MEN1 tumor suppressor gene on 11q13 that produces menin, has a prevalence of 1:20,000 to 40,000, and can present with combinations of over 20 different endocrine and non-endocrine tumors.[2-5]

MEN2A and 2B are due to gain of function mutations in the RET proto-oncogene (10q11.21), have a prevalence of 1:35,000 to 40,000, and have medullary thyroid carcinoma (MTC) as a defining malignancy. The rate at which MTC develops in MEN2 is dependent on the specific allele involved.[1-3]

The current literature is sparse regarding head and neck neoplastic manifestations in pediatric MEN.

## Methods

Objective: To examine the neoplastic and endocrine manifestations of MEN syndromes in the pediatric head and neck.

- Chart review was completed of pediatric patients at Children's Hospital of Colorado (CHCO) between January 1, 2005 and June 1, 2022, and received Colorado Multiple Institutional Review Board approval (COMIRB #20-2009).
- Patients with genetic mutations associated with MEN syndromes were cross referenced with those diagnosed with head and neck tumors.
- Outcome measures included demographic/clinical data, clinical course, tumor and germline genetics, and relevant imaging and pathology data.

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## Results

Fifty-three patients were identified with genetically confirmed MEN (fifteen MEN1, thirty-four MEN2A, and four MEN2B) and 3 patients were identified with clinical diagnoses of MEN1 (Figure 1). Thirty-three (59%) patients in this cohort required head and neck procedures, while 23 patients (41%) did not undergo surgical intervention and received routine surveillance. Thyroid malignancies were identified in 36% (9/25) of thyroidectomy specimens (21 MEN2A, 4 MEN2B), with medullary thyroid carcinoma (MTC) present in five MEN2A patients and three MEN2B patients (89%), and papillary thyroid carcinoma (PTC) present in one MEN2A patient (11%) (Table 2). Nearly 90% (8/9) of thyroid malignancies were occult, with some occurring earlier than predicted by current guidelines. Of the eight MEN1 parathyroidectomy patients, four demonstrated parathyroid hyperplasia and four presented with parathyroid adenoma. Neck dissections were performed in 24% (2 MEN1, 2 MEN2A, and 4 MEN2B), with two MEN2B (50%) demonstrating occult cervical lymph node (LN) metastases. The remaining neck dissections were disease free. Additional histopathologic findings included C-cell hyperplasia in 57% (12/21) of MEN2A thyroidectomy patients. Molecular testing was available in twenty-eight (28/33, 84%) surgical patients, with the most common mutation being p.C609Y (c.1826G>A) in the RET gene (8/28, 29%). The p.C634R (c.1900T>C) RET gene mutation was associated with the greatest number of malignancies (3/28, 11%) – all MTC. The p.Arg516Profs*15 (c.1546dup), Phe134fs (c.402delC), and p.Tyr227* (c.681C>G) mutations were associated with parathyroid adenoma. No surgical complications were reported and there were no known fatalities or need for adjuvant chemotherapy or radiation therapy. Demographics of the surgical patients are described in Table 1.

Figure 1: Surgical vs. Non-Surgical MEN Patients

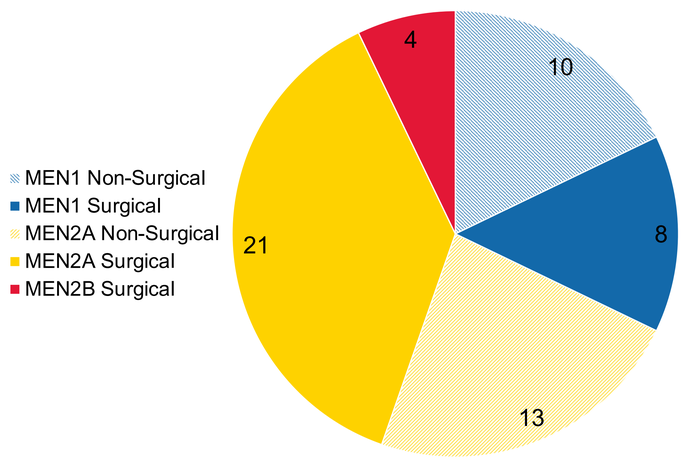


Table 1: Surgical Patient Data

| | |
|---|---|
| **Total** | **33** |
| **Male : Female** | 1.06 : 1 |
| **Ethnicity/Race:** | |
| White | 26 (79%) |
| Hispanic | 5 (15%) |
| Black | 0 (0%) |
| Asian | 0 (0%) |
| Native American | 5 (15%) |
| Other | 0 (0%) |
| **Family history of MEN** | 32 (97%) |
| **Family history of cancer** | 31 (94%) |
| **Mean age at initial presentation to CHCO** | 8.9 years (SD 5.0) |
| **Mean age at surgical intervention** | 9.8 years (SD 4.8) |
| MEN1 Patients | 12.7 years (SD 3.6) |
| MEN2A Patients | 8.7 years (SD 5.0) |
| MEN2B Patients | 8.7 years (SD 2.1) |

Table 2: Multiple Endocrine Neoplasia Syndrome Patients with Disease on Pathology

| | MEN Subtype | Sex | Age at Presentation (years) | Age at Diagnosis (years) | Tumor Pathology | Mutation | ATA Risk Category | Incidental Finding? | C Cell Hyperplasia? |
|---|---|---|---|---|---|---|---|---|---|
| 1 | MEN2A | Female | 1.45 | 3.37 | Medullary thyroid carcinoma | p.C609Y c.1826G>A | ATA-MOD | Yes | Yes |
| 2 | MEN2A | Male | 1.05 | 4.15 | Medullary thyroid carcinoma | p.C634R c.1900T>C | ATA-H | Yes | Yes |
| 3 | MEN2A | Male | 8.63 | 8.90 | Medullary thyroid carcinoma | p.C634R c.1900T>C | ATA-H | Yes | Yes |
| 4 | MEN2A | Female | 18.46 | 16.22 | Medullary thyroid carcinoma | p.C634W c.1902C>G | ATA-H | Yes | No |
| 5 | MEN2A | Male | 7.88 | 8.04 | Medullary thyroid carcinoma | p.C634R c.1900T>C | ATA-H | Yes | Yes |
| 6 | MEN2B | Female | 6.27 | 6.34 | Medullary thyroid carcinoma | p.M918T c.2753T>C | ATA-HST | Yes | No |
| 7 | MEN2B | Female | 11.76 | 11.89 | Medullary thyroid carcinoma | p.M918T c.2753T>C | ATA-HST | No | No |
| 8 | MEN2B | Male | 8.97 | 8.96 | Medullary thyroid carcinoma | Unknown | Unknown | Yes | Yes |
| 9 | MEN2A | Female | 12.30 | 12.62 | Papillary thyroid carcinoma | p.C609Y c.1826G>A | ATA-MOD | Yes | No |
| 10 | MEN1 | Female | 17.40 | 17.02 | Parathyroid adenoma | p.Arg16Profs*15 c.1546dup | N/A | Unknown | No |
| 11 | MEN1 | Male | 10.47 | 11.42 | Parathyroid adenoma | p.Phe134fs c.402delC | N/A | Unknown | No |
| 12 | MEN1 | Male | 7.32 | 11.98 | Parathyroid adenoma | p.Phe134fs c.402delC | N/A | Unknown | No |
| 13 | MEN1 | Male | 6.72 | 9.08 | Parathyroid adenoma | p.Tyr227* c.681C>G | N/A | Unknown | No |

## Conclusions

Endocrine tumors of the head and neck are common and early manifestations in children with MEN syndromes, especially in those with high-risk subtypes of MEN2.

Occult disease is a possibility even in young children, with MEN2A children in moderate and high-risk categories possessing the capacity to develop early and varied forms of head and neck neoplastic disease relative to the current guidelines. Children with MEN2B have higher risk for occult locoregional disease at the time of presentation.

Surgical intervention with parathyroidectomy in MEN1 patients with primary hyperparathyroidism (PHPT) is an important aspect of management. Prophylactic thyroidectomy in MEN2 patients can lead to early diagnosis of malignancy and prevent precancerous C-cell hyperplasia from progressing.

## Implications

Current MEN surveillance guidelines differ based on subtype. Parathyroid adenoma and PHPT screening for MEN1 is recommended starting at age 8. MEN2 recommendations largely depend on the risk associated with the specific RET mutation, with the most common screening tool being prophylactic thyroidectomy.[2,3]

These findings support the use of early prophylactic surgery in the management of MEN patients, especially those with moderate and high-risk MEN2A. Pediatric thyroid or parathyroid disease, particularly malignancy, in a child not previously diagnosed with a hereditary cancer disorder should raise concern for an MEN syndrome and prompt multidisciplinary workup.

## Disclosures

No disclosures to report.

## References

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