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Coexistence of Slipped Capital Femoral Epiphysis and multiple endocrine neoplasia type 2B (MEN2B) - a case report

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Abstract

Introduction: MEN 2B syndrome is distinguished by the occurrence of medullary thyroid cancer, pheochromocytoma, mucosal neuromas, marfanoid features, and skeletal anomalies, including kyphoscoliosis, joint laxity, pes cavus, and, in a smaller number of cases, slipped capital femoral epiphysis (SCFE).
Case report: We describe a case report of a 15-years-old patient with the diagnosis of the MEN2B syndrome with a rare manifestation of Slipped Capital Femoral Epiphysis (SCFE). A 15-year-old female presented to the orthopedics out-patient department (OPD) with complaints of pain around the right hip and knee and walking with a limp for approximately four months. Additionally, the feeling of enlarged thyroid gland was reported. X-ray confirmed the presence of the SCFE, while thyroid biopsy revealed the presence of medullary thyroid cancer (MTC). Thus, the diagnosis of MEN2B was made.

Conclusion: Slipped capital femoral epiphysis (SCFE) can occasionally be a manifestation of MEN 2B syndrome. It is important for physicians to be aware of this association, as it can contribute to the early detection of a potentially life-threatening condition.
Keywords: MEN2B, SCFE, Slipped Capital Femoral Epiphysis, Medullar Thyroid Cancer, MTC, Marfanoid habitus

Introduction

Multiple endocrine neoplasia type 2 (MEN2) is a rare congenital disorder with estimated prevalence between 1 in 600,000 to 1 in 4 million. Sipple's 1961 report highlighted the significant link between bilateral pheochromocytomas and medullary thyroid cancer (MTC), leading to the identification of MEN2. Subsequent studies further revealed the involvement of non-traditional endocrine tissues like the gastrointestinal tract and skin in this syndrome [1]. It is characterized by the development of tumors in endocrine organs, primarily in the thyroid, parathyroid glands, and adrenal glands [2].

MEN2 is divided into three types: MEN1 - a rare syndrome characterized by primary hyperparathyroidism, pituitary adenomas, and neuroendocrine tumors of the pancreas and gastrointestinal tract [3]. MEN1 can predispose individuals to the development of both endocrine and non-endocrine tumors, such as skin tumors, central nervous system tumors, and breast tumors [4]. MEN 2A, also known as Sipple's syndrome, is inherited in an autosomal dominant manner and accounts for 60-80% of cases. It is characterized by medullary thyroid carcinoma, pheochromocytoma of the adrenal glands, and primary hyperparathyroidism [5]. MEN 2B is characterized by medullary thyroid carcinoma, pheochromocytoma of the adrenal medulla, a marfanoid body habitus, and neurological abnormalities such as mucosal neuromas. Gangliomatosis of the gastrointestinal tract and its complications may also occur in these patients. Moreover, skeletal system changes, including kyphoscoliosis, increased joint mobility and laxity, pes cavus, and rarely slipped capital femoral epiphysis (SCFE) , are also possible manifestations in MEN2B patients [6].

The diagnosis of this medical condition remains challenging due to its ambiguous clinical presentation and possible symptoms from various systems, which may not always occur in a typical combination. To this date there is only a small number of described cases of young patients with MEN2-b with skeletal manifestation. For this reason, we think it is important to emphasize the importance of knowledge of the characteristics of the MEN2-b syndrome in order to make a quick diagnosis and implement appropriate treatment.

Here, we want to present a case of MEN2-b in young patient diagnosed in the course of SCFE based on the laboratory tests and morphogenic features.

Case Report

A 15-year-old female patient presented to the orthopedics out-patient department with right knee and hip pain persisting for approximately 4 months, previously managed on an outpatient basis with physical therapy but without undergoing X-ray examination. X-ray

imaging of the hip joints (Figure 1) was performed on the admission, 3 months after the onset of symptoms and revealed long, slender limbs with excessive laxity (Marfanoid features).

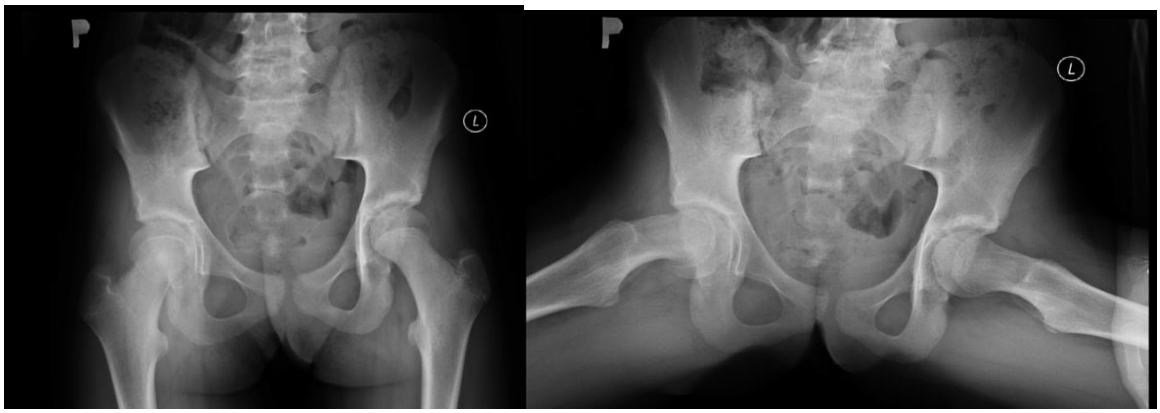


Figure 1.

Radiograph (anteroposterior (AP) and frog view of 15 year-old female patient.

Clinical examination revealed: flexion 90 degrees, abduction 40 degrees, adduction 30 degrees, internal rotation -10 degrees, external rotation 45 degree. Upon admission, the patient was referred for an endocrinological consultation, which revealed thyroid enlargement. According to the patient, the feeling of increase in size of the thyroid gland has been present for 3-4 months. The measured blood pressure was within the normal range. Based solely on morphological characteristics, the suspicion of medullary thyroid carcinoma was raised.

Laboratory results (Table 1) revealed a normal hematological profile, and various parameters including blood sugar, blood urea, serum creatinine, parathyroid hormone, procalcitonin, thyroid-stimulating hormone (TSH), alkaline phosphatase and serum calcium were all within the normal range. Serum levels of procalcitonin were significantly elevated and FT4 was slightly raised.

Thyroid ultrasound examination (Figure 2) revealed hypoechoic nodules in both lobes of the thyroid. A fine-needle aspiration biopsy of the thyroid was performed, confirming the presence of medullary thyroid carcinoma.

	Result	Range of reference
Parathyroid hormone	40,66 pg/ml	15-65 pg/ml
Procalcitonin	4,09 ng/ml	0-0,5 ng/ml
Free Thyroxine	1,72 ng/dl	0,98-1,63 ng/dl
Thyroid Stimulating Hormone	0,759 nIU/ml	0,51-4,3 nIU/ml
Vitamin D	17,9 ng/ml	20-60 ng/ml
Alkaline phosphatase	164 U/l	110-369 U/l
Serum Calcium	9,3 mg/dl	8,6-10,6 mg/dl

Table 1.

Laboratory test results by 15 years-old female patient

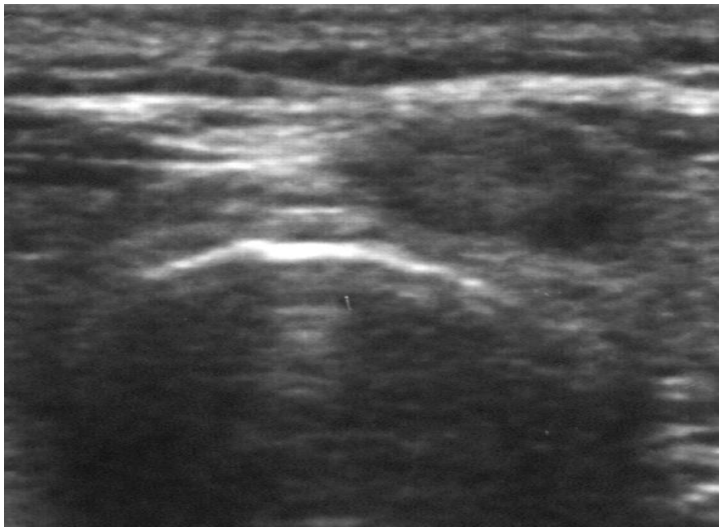


Figure 2.

Thyroid ultrasound image. Ultrasonography of the anterior neck showed well-defined, heterogeneous, predominantly hypoechoic round lesions in both the lobes of thyroid.

Based on the presence of medullary thyroid carcinoma confirmed by biopsy, ganglioneuromatosis-like changes in the lips and tongue, marfanoid body habitus, and the occurrence of Slipped Capital Femoral Epiphysis in the patient, the diagnosis of Multiple Endocrine Neoplasia type 2B (MEN-2B) has been established.

Due to the SCFE causing a 60-degree displacement of the right hip, the patient was deemed eligible for surgical treatment. Surgical hip dislocation with osteotomy of the right femoral head was performed, along with prophylactic stabilization of the left femoral head (Figure 3). A correction of the displacement was achieved by eliminating retroversion of the femoral head.

On the 10th day postoperative, the patient was transferred to the Oncology Center for further treatment. During the oncological treatment, the patient underwent two additional surgeries, including total thyroidectomy with bilateral lymph node resection (Figure 4). The patient's family members (parents and siblings) are under the care of the oncology outpatient clinic, and currently, there are no signs of thyroid tumor recurrence.

Figure 3.
Intraoperative photo during surgical hip dislocation

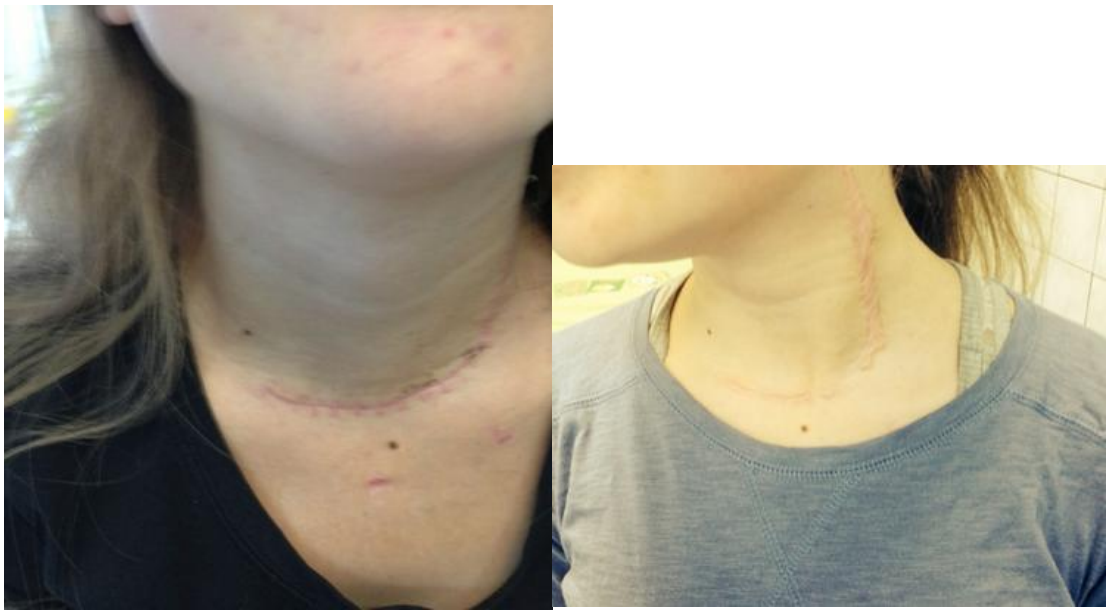
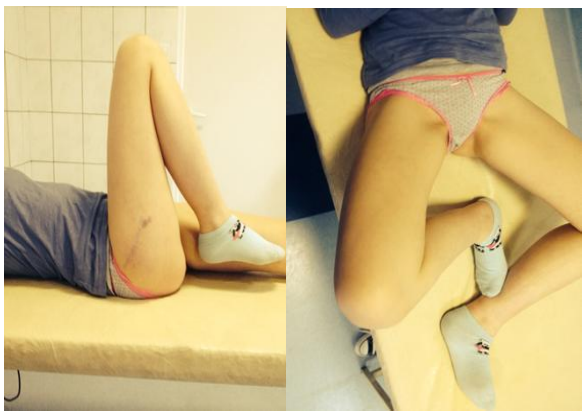


Figure 4.
Postoperative photograph after total thyroidectomy and lymphadenectomy

10 months after applied treatment, the young patient did not report any pain symptoms, moved herself with full weight-bearing.
The only observed limitation was reduced internal rotation of the right hip (20 degrees) (Figure 5). In the follow-up X-ray of the hip joints after surgical treatment, no signs of avascular necrosis (AVN) of the head of femur were seen (Figure 6).



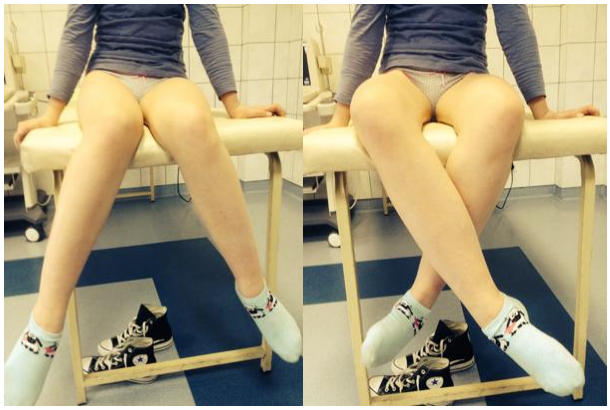


Figure 5.
Photos showing range of motion 10 months after surgical treatment of SCFE by the 15 years old patient

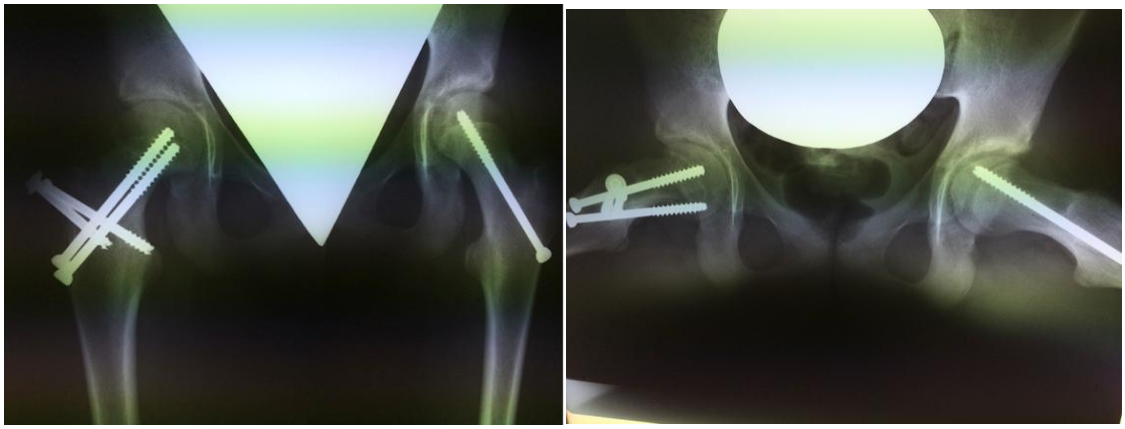


Figure 6.
Radiograph (anteroposterior and frog view) 10 months after surgical treatment of SCFE by the 15 years old patient

Discussion

MEN 2B also called Wagenmann-Froboese or mucosal neuroma syndrome was first described in 1961 [7]. According to the literature MEN2A syndrome affects 60% to 90% of MEN2 families while MEN2B affects only 5% of MEN2 families [8]. Medullary thyroid carcinoma (MTC) originates from the C cells (which secrete calcitonin) of the thyroid gland. The hereditary forms of MTC are associated with MEN2B, which is caused by a germline mutation in the RET proto-oncogene [9]. So far, The mutation of exon 16 of the RET proto-oncogene located on chromosome 10 is reported in 95% of MEN2 cases. However, there have also been described cases negative for RET mutation and that may also increase an individual's likelihood of developing the disease [10]. According to the literature, the approximate mean age for the diagnosis of MEN2B syndrome is 11.5 years [11].

MTC, a form of thyroid cancer, is the most common and usually the first observed manifestation in individuals with MEN2A and MEN2B. It is present in all affected individuals, with a complete penetrance rate of 100%. The typical presentation of MTC often involves a solitary thyroid nodule and/or cervical lymphadenopathy [12].

Pheochromocytoma is also a very important factor that occurs in patients with MEN2B. The incidence rate has been described as 50% by the patients with MEN2B [13]. Usually it occurs around 30 years. Complete manifestations including pheochromocytoma, MTC and mucosal neuromas may be observed in 50% of the patients.

The ophthalmological manifestations include ptosis, conjunctivae, dryness of the eye, photophobia, neuromas of the eyelid, increased inta-ocular pressure (IOP), enlarged perilimbal conjunctival vessels. These have been described among 86% at the time of the diagnosis [14, 15]. Another typical findings for MEN2B are mucosal neuromas of tongue, lips, inner eyelids, tongues, which have been described as almost pathognomonic in the literature among patients with MEN2b in the presence of MTC [16]. However in our patient these changes were absent.

The occurrence of SCFE as an initial manifestation of MEN 2B has been exceptionally rare and has been scarcely documented in existing literature [17, 18]. Symptoms such as hip pain, knee pain, and limping do not always indicate a SCFE, however, X-ray examination allows for the diagnosis of this entity, like in our case. One study found that a decrease in growth hormone and an increase in estrogen enhance the shear strength of the proximal tibial physeal plate. It concluded that an imbalance with higher growth hormone levels relative to estrogen could potentially increase the risk of slipping [19]. SCFE occurs among children with endocrinopathies such as thyroid disorders including hypothyroidism and hyperthyroidism, hyperparathyroidism, pituitary insufficiency as well as hypogonadal states [20]. Due to its rarity in patients with MEN2B the exact incidence of this association cannot be determined.

Marfanoid habitus in patients with MEN2B syndrome resembles patients with Marfan syndrome, whose symptoms include excessive laxity, long limbs, and tall stature. According to Castinetti's largest cohort study to date (n=345), a Marfanoid habitus was observed in 73% of the participants [21].

The management of MEN 2B is a challenging task that demands effective coordination among various healthcare professionals. A multidisciplinary approach involving medical, surgical, and oncologic interventions is crucial and should be tailored to meet the specific requirements of each patient. The recommended approach in management among patients with MEN2B includes total thyroidectomy and lymph node dissection of the central and when it is needed, lateral compartment of the neck. In all patients after total thyroidectomy, the lifelong L-Thyroxine replacement therapy, as well as the regular calcitonin and carcinoembryonic antigen (CEA) determination should be implemented [22]. Adrenal cortex-sparing surgery is recommended among patients, with diagnosed pheochromocytoma. Among those without adrenal changes at the time of diagnosis, screening is required [23].

Conclusion

In summary, a patient presenting with hip pain should be approached comprehensively. If the physician notices excessive joint laxity, long limbs, tall stature, and concurrent thyroid enlargement, it is important to promptly refer the patient to an endocrinologist to exclude the

presence of MEN2B syndrome. Accurately diagnosing the condition allows for early implementation of appropriate treatment, which significantly impacts the outcomes of the therapy and improves the quality of life and comfort for the young patient and their family.

Author Contributions

Conceptualization, K.K., I.M., M.B.; supervision and project administration, M.B., K.K., I.M., A.A., J.Z.; T.H.A and A.A.A., I.M., K.K.; Methodology, K.K., I.M.; Software, A.A., J.Z.; Validation, K.K., I.M.; formal analysis, A.A., M.B.; investigation, M.B.; resources, K.K., I.M.; writing- original draft preparation, K.K., I.M., A.A., J.Z., M.B.; writing- review and editing and visualization, K.K., I.M., A.A., J.Z., M.B.

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Institutional Review Board Statement

Not applicable. The study was conducted in accordance with the Declaration of Helsinki. In accordance with the law in force in the Republic of Poland, case report retrospective studies do not require the opinion or consent of the Bioethics Committee, as they are not a medical experiment in which human organisms would be interfered with. For this reason, we did not seek the consent of the Commission. What's more, the results of the study did not affect the management of patients at any stage, so the above-mentioned procedure was followed.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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