Neuroimmunology Reports 2 (2022) 100080

Contents lists available at ScienceDirect

Neuroimmunology Reports

journal homepage: www.elsevier.com/locate/nerep

# Multiple sclerosis following multiple endocrine neoplasia type 2: A case report

Behnaz Sedighi[a], Mohammadhossein Gozashti[b], Zahra Akbari[c], Mohammad Shafie'ei[c], Zohreh Abna[d,*]

[a] Associate Professor of Neurology, Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran
[b] Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[c] Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[d] MS Fellowship, Department of Neurology, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

*Keywords:*
Multiple sclerosis
Multiple Endocrine Neoplasia
Rare disorders

ABSTRACT

*Background:* MEN is a disorder characterized by the involvement of two or more endocrine glands by tumors. Mutations in RET proto-oncogene on the tenth chromosome have been established as the genetic factor in the disease's pathogenesis. Out of MEN's four different subtypes, MEN 2 manifests with medullary thyroid carcinomas, pheochromocytomas, and parathyroid tumors. Multiple Sclerosis(MS) is an autoimmune disease of the central nervous system leading to demyelination and axonal loss.

*Case description:* Our patient, an adult female with a past medical history of Multiple Endocrine Neoplasia(MEN) Type II, was admitted to the care center with complaints of blurred vision, color perception changes, ocular movement pain, and paresthesia. She was then diagnosed with Multiple Sclerosis after confirmatory diagnostic criteria were met.

*Conclusion:* With an unknown etiology and many different environmental factors to blame, about 200 genes have been associated with MS's pathogenesis. Because the RET gene is also expressed in the CNS, mutations in the gene, as in the MEN disorder, can be hypothesized to predispose an individual to MS.

## Introduction

Associations between Multiple Endocrine Neoplasia(MEN) & the occurrence of Multiple Sclerosis(MS) have not been established to date. Only two cases have reported an association of MEN manifestations (e.g., Medullary Thyroid Carcinoma) with MS, of which only one was accessible (López Domínguez et al., 1997; Sirbu et al., 2020). Here, we present a case of a 30-year-old female admitted to the care center due to complaints of blurred vision and paresthesia in all four extremities.

## Case report

A 30-year-old female was admitted to the clinic due to left eye blurred vision which had progressed for ten days. She did not report any pain at rest or during eye movement, but the color vision was impaired. There was no history of headache, nausea, vomiting, or recent head trauma. She noted a history of abortion two months earlier, after which she realized a new-onset gait imbalance that continued to the present. The patient also complained of paresthesia in all extremities since a year prior, for which she did not seek medical care. She had a history of total thyroidectomy, with a diagnosis of medullary thyroid carcinoma 20 years ago. Besides, during her first pregnancy, she was diagnosed with bilateral pheochromocytoma and underwent bilateral adrenalectomy after delivery. Furthermore, she had a history of hyperparathyroidism two years ago, for which she underwent total parathyroidectomy.

She took Prednisolone 5 mg daily, Fludrocortisone 0.1 mg daily, Levothyroxine 100 $\mu$g daily, Citalopram 20 mg daily, and Supplementary Calcium and Vitamin D tablets.

She had a family history of pheochromocytoma and thyroid carcinoma in both of her sisters. Furthermore, her mother had hyperparathyroidism, unilateral pheochromocytoma, and total thyroidectomy.

On systemic physical examination, the vital signs were within the normal ranges. There were no signs of lymphadenopathy in any of the lymphatic chains on the head and neck, with no neck stiffness also being detected. In addition, there was no visible pallor, icterus, or conjunctivitis. Moreover, the chest and abdominal cavity examinations revealed no significant abnormal findings(e.g., hepatosplenomegaly). There was no cyanosis, edema, or clubbing in any of her four extremities.

* Corresponding author.
*E-mail addresses:* behnaz.sedighi@gmail.com (B. Sedighi), drgozashti@yahoo.com, gozashti@kmu.ac.ir (M. Gozashti), zahraakbari75@yahoo.com (Z. Akbari), ms6584@gmail.com (M. Shafie'ei), abna.zohreh90@yahoo.com (Z. Abna).

https://doi.org/10.1016/j.nerep.2022.100080
Received 1 January 2022; Accepted 12 February 2022

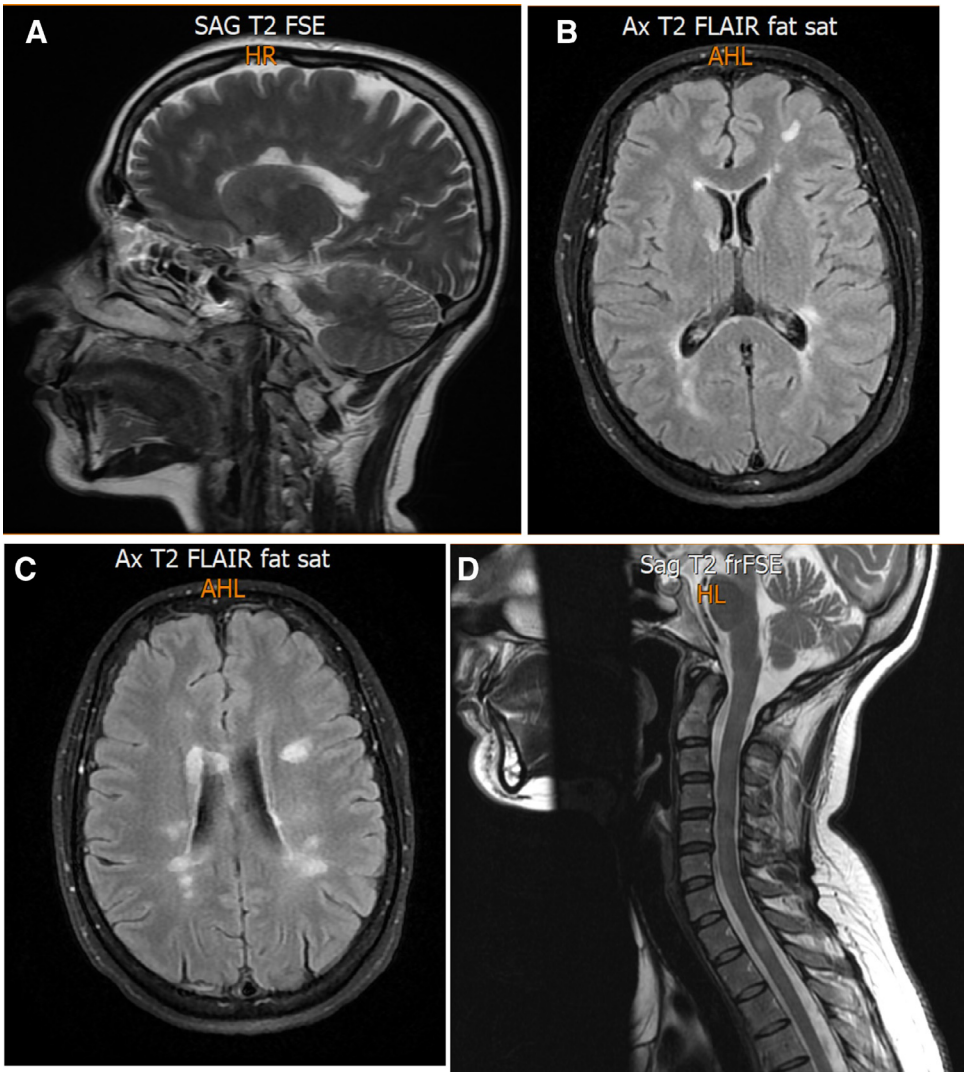


**Fig. 1.** A, B, C, D - Contrast-enhanced Brain and Cervical MRI during admission.

On neurologic examination, she was alert and oriented. Examination of the cranial nerves mainly revealed no abnormalities, except for visual acuity in the left eye, which was determined to be 4/10. Pupils were mid-size and reactive to light, but Marcus Gunn was detected in the left eye. The fundoscopic examination revealed normal optic discs without papilledema. Motor examination showed normal strength in the proximal and distal extremities. However, Deep Tendon Reflexes (DTRs) showed generalized hyperreflexia, and plantar reflexes were extensors on both sides. Examinations regarding motor coordination showed dysmetria on the Finger-to-Nose and Heel-to-Shin tests on both sides. Tandem gait was impaired. Sensory examinations revealed impaired position and vibration sense in both lower extremities, and the Romberg sign was positive.

Laboratory data showed normal values/levels of complete blood cell count (CBC), blood sugar, urea, and creatinine; Serum electrolytes including sodium, potassium, Ionized, and Total Calcium and Phosphorus were in the normal range. Also, liver and thyroid function tests were within normal ranges.

Vasculitis tests (i.e., ANA, Anti ds DNA, ANCA) returned negative for abnormalities. However, abnormal levels of Vitamin-D (12.7 ng/ml), Parathyroid Hormone (PTH) (91 pg/ml), and Vitamin B12 (164 pg/ml) were detected.

The lumbar puncture was performed in the patient for cerebrospinal fluid (CSF) analysis; Normal values of white and red blood cells, glucose, and proteins were detected. Compared with serum, a higher than the threshold number of oligoclonal bands was seen.

Brain and cervical spine MRI with and without contrast enhancement was also performed. Multiple T2 hyperintense foci were detected in the periventricular, juxtacortical, and infratentorial (brainstem and cerebellum) regions. After gadolinium injection, enhancement was not detected in any of the lesions. Cervical MRI showed multiple areas of abnormal signaling in the cervical cord without enhancements (Fig. 1).

The patient underwent complementary diagnostic imaging tests, including abdominal sonography. There were no significant abnormal findings except for polycystic ovaries and multiple small gallbladder stones.

Ultimately, a 5-day pulse therapy regime with glucocorticoid (intravenous methylprednisolone, 1 gr) was initiated for the patient, leading to a relative improvement in the symptoms, especially the vision. Then, maintenance therapy with interferon $\beta$1b was established, during which she is routinely visited and is currently asymptomatic.

## Discussion

Multiple Endocrine Neoplasia(MEN) is an autosomal dominant or sporadic disorder characterized by at least two endocrine glands' involvement by tumors. This disease is classified into four different sub-

types: MEN 1–4. Out of the four mentioned, MEN 2 or Sipple's syndrome manifests with medullary thyroid carcinomas(MTC), pheochromocytomas, and parathyroid tumors(or primary hyperparathyroidism as stated by different authors). It consists of three different subtypes itself, namely MEN 2A, 2B(which is also sometimes referred to as MEN 3), and Familial Medullary Thyroid Carcinoma(FMTC) (Wells et al., 2015; Jameson et al., 2018; Donis-Keller et al., 1993; Hofstra et al., 1994; Mulligan et al., 1994; Mulligan and Ponder, 1995; Al-Salameh et al., 2018).

A RET proto-oncogene mutation on Chromosome 10 has been established as the underlying genetic factor in the disease's pathogenesis, with 50 mutations reported. Furthermore, MEN 2A and FMTC have been associated with mutations in the Cysteine-rich extracellular domain, with codon 618 being the most frequent. In contrast, MEN 2B/3 has been associated with mutations on the codon 918 of the intracellular tyrosine kinase domain (Jameson et al., 2018; Frank-Raue et al., 2010). Based on the points mentioned above, sequencing of exons 10 and 11 should be carried out. If the results turned out negative, the sequencing should continue to exons 8, 13, 14, 15, and 16 in order (Wells et al., 2015).

Multiple Sclerosis(MS) is a chronic autoimmune disease of the CNS system, leading to inflammation, demyelination, and axonal loss of the system's neurons (Compston and Coles, 2008). It has been estimated that overall, about two to three million individuals currently are suffering from the disease, with different studies mentioning different rates ranging from 33 to 300 individuals per 100,000 of the population (Browne et al., 2014; Eskandarieh et al., 2016).

Genetically, about 200 genes have been associated with the pathogenesis of MS in different studies, with some noting the HLA(human)complex, assigning 20–30 percent of the susceptibility to itself(HLA DRB *15:01 being mentioned as the most common one of the HLA involved in those affected) (Haines et al., 1998; Patsopoulos et al., 2013).

Associations between any of the manifestations of MEN & the occurrence of MS have not been established to date. However, based on different studies, the RET gene is expressed in peripheral and central nervous systems (Avantaggiato et al., 1994; Pachnis et al., 1993; Schuchardt et al., 1994). Therefore, we can hypothesize that a mutation in the RET gene might predispose an individual to MS. We could only find one study, published in 1997 by López Domínguez et al., that has tried to report such a connection. However, there was no access to the article's manuscript (López Domínguez et al., 1997).

Vice versa, in a case report by Sirbu et al. in 2020, Romania, a 46-year-old female diagnosed with MS in 2008 (with the necessary diagnostic features being met), was found to have been suffering from thyroid collision tumors (confirmed as both medullary and papillary thyroid carcinoma). However, the diagnosis of multiple endocrine neoplasia was ruled out via appropriate paraclinical studies, and the patient underwent total thyroidectomy and compartment lymph node dissection. Also, she had positive serology, indicating infection with EBV (Sirbu et al., 2020).

With the MEN and MS correlation hypothesis in mind, we recommend future studies to evaluate the possible genetic mechanism(s) in play. If such mechanisms are then detected, we can safely presume that the evidence would vastly broaden the knowledge regarding the pathophysiology of both of the disorders.

## Declaration of Competing Interest

The authors declare that no conflict of or competing interests existed or occurred in this manuscript.

## Acknowledgments

None

## Funding

No funding or sponsorship was received for the conduction of this study.

## Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

## Ethics approval

No ethical approval was required as this manuscript is a case report. However, the necessary written informed consent was obtained from the patient herself.

## Availability of data and materials

The dataset supporting the conclusions of this article is available upon request to the corresponding author, Zohreh Abna.

## References

Al-Salameh, A., Baudry, C., Cohen, R., 2018. Update on multiple endocrine neoplasia Type 1 and 2. Presse Med. 47 (9), 722–731.
Avantaggiato, V., Dathan, N.A., Grieco, M., Fabien, N., Lazzaro, D., Fusco, A., et al., 1994. Developmental expression of the RET protooncogene. Cell Growth Different. 5 (3), 305–311.
Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B.V., et al., 2014. Atlas of Multiple Sclerosis 2013: a growing global problem with widespread inequity. Neurology 83 (11), 1022–1024.
Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet 372 (9648), 1502–1517.
Donis-Keller, H., Dou, S., Chi, D., Carlson, K.M., Toshima, K., Lairmore, T.C., et al., 1993. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. Hum. Mol. Genet. 2 (7), 851–856.
Eskandarieh, S., Heydarpour, P., Minagar, A., Pourmand, S., Sahraian, M.A., 2016. Multiple sclerosis epidemiology in East Asia, South East Asia and South Asia: a systematic review. Neuroepidemiology 46 (3), 209–221.
Frank-Raue, K., Rondot, S., Raue, F., 2010. Molecular genetics and phenomics of RET mutations: impact on prognosis of MTC. Mol. Cell. Endocrinol. 322 (1–2), 2–7.
Haines, J.L., Terwedow, H.A., Burgess, K., Pericak-Vance, M.A., Rimmler, J.B., Martin, E.R., et al., 1998. Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity. The multiple sclerosis genetics group. Hum. Mol. Genet. 7 (8), 1229–1234.
Hofstra, R.M., Landsvater, R.M., Ceccherini, I., Stulp, R.P., Stelwagen, T., Luo, Y., et al., 1994. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. Nature 367 (6461), 375–376.
Jameson, J.L., Fauci, A.S., Kasper, D.L., Hauser, S.L., Longo, D.L., Loscalzo, J., 2018. Harrison's Principles of Internal Medicine. McGraw-Hill Education, New York [etc.].
López Domínguez, J.M., Blanco Ollero, A., Casado Chocán, J.L., Díaz Espejo, C., 1997. Multiple sclerosis and multiple endocrine neoplasia type 1. Neurologia 12 (6), 267–268.
Mulligan, L.M., Eng, C., Healey, C.S., Clayton, D., Kwok, J.B., Gardner, E., et al., 1994. Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat. Genet. 6 (1), 70–74.
Mulligan, L.M., Ponder, B.A., 1995. Genetic basis of endocrine disease: multiple endocrine neoplasia type 2. J. Clin. Endocrinol. Metab. 80 (7), 1989–1995.
Pachnis, V., Mankoo, B., Costantini, F., 1993. Expression of the c-ret proto-oncogene during mouse embryogenesis. Development 119 (4), 1005–1017.
Patsopoulos, N.A., Barcellos, L.F., Hintzen, R.Q., Schaefer, C., van Duijn, C.M., Noble, J.A., et al., 2013. Fine-mapping the genetic association of the major histocompatibility complex in multiple sclerosis: HLA and non-HLA effects. PLoS Genet. 9 (11), e1003926.
Schuchardt, A., D'Agati, V., Larsson-Blomberg, L., Costantini, F., Pachnis, V, 1994. Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase receptor Ret. Nature 367 (6461), 380–383.
Sirbu, A.M., Sirbu, C.A., Eftimie, L., Soare, A.M., Ghinescu, M.C., Ionita-Radu, F., 2020. Multiple sclerosis, human herpesvirus 4 and thyroid collision tumor: a case report. Exp. Ther. Med. 20 (4), 3458–3461.
Wells Jr., S.A., Asa, S.L., Dralle, H., Elisei, R., Evans, D.B., Gagel, R.F., et al., 2015. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 25 (6), 567–610.