A Rare Co-Existence of Multiple Cerebral Cavernous Malformations and Pleomorphic Adenoma of the Parotid Gland in Myotonic Dystrophy

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ABSTRACT

Myotonic dystrophy is an autosomal dominant inherited disorder primarily affecting muscle function. Myotonia, progressive muscle weakness and wasting, and associated systemic involvement, *i.e.*, cataracts, cardiac conduction defects and endocrine abnormalities especially insulin resistance, are the characteristic features. Recent evidence has shown an increased risk of developing benign as well as malignant tumours in such patients. We report a 39-year male of myotonic dystrophy who presented with multiple cerebral cavernous malformations in addition to pleomorphic adenoma of the parotid gland. Though the association of myotonic dystrophy with salivary gland neoplasms has been sparsely documented in the literature, but the co-existence with multiple cerebral cavernous malformations has not been reported so far. Our case is the first of its kind.

Key Words: *Cerebral cavernous malformations, Myotonic dystrophy, Parotid gland, Pleomorphic adenoma.*

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INTRODUCTION

Myotonic dystrophy or dystrophia myotonica (DM) has two types; DM1, which is caused by an unstable tri-nucleotide repeat expansion in the DMPK gene and DM2, which is caused by an unstable tetra-nucleotide repeat expansion in CNBP gene.[1] Common manifestations are myotonia, progressive muscle weakness / wasting, and systemic abnormalities, such as, intellectual disability, cardiac conduction defects, endocrine disturbances, gastrointestinal problems and cataracts.[1,2] Recent evidence has shown an increased risk of developing benign as well as malignant tumours in DM1.[3-5] Though the association of DM1 with salivary gland neoplasms is sparsely documented in the literature, but co-existence with multiple cerebral cavernous malformations has not been reported so far. To the best of our knowledge, this is the first case of DM showing the co-existence of multiple cerebral cavernous malformations and parotid gland pleomorphic adenoma.

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CASE REPORT

A 39-year male, diabetic, presented with progressive history of difficulty in holding objects in both hands for several years, and difficulty in swallowing for many months. His history was significant for occasional generalised tonic-clonic (GTC) seizures. He was married for 14 years with no children. He was a non-smoker and non-alcoholic. His father had similar complaints of difficulty holding objects in his both hands and releasing his grip, but he had never sought any medical consultation and died of sudden cardiac arrest at the age of 45 years.

On examination, he had nasal voice, elongated face with frontal baldness and temporo-mandibular wasting, and right parotid swelling (Figure 1, A and B). He had moderate weakness in the facial and bulbar muscles; 4/5 power in the muscles of both forearms and 3/5 power in the intrinsic muscles of both hands with positive action and percussion myotonia. He had bilateral posterior sub-capsular cataracts on slit-lamp examination. On investigations, serum creatine kinase (CK) level was 509 U/L. Electrocardiography (ECG) showed a left bundle branch block (LBBB), and electromyography (EMG) confirmed myotonic discharges and myopathic motor units. Fine needle aspiration cytology (FNAC) of the parotid swelling reported pleomorphic adenoma. Brain magnetic resonance (MR) imaging with gadolinium enhancement demonstrated multiple characteristic 'popcorn-like' lesions called cerebral cavernous malformations (CCMs) (Figure 2, A - D).

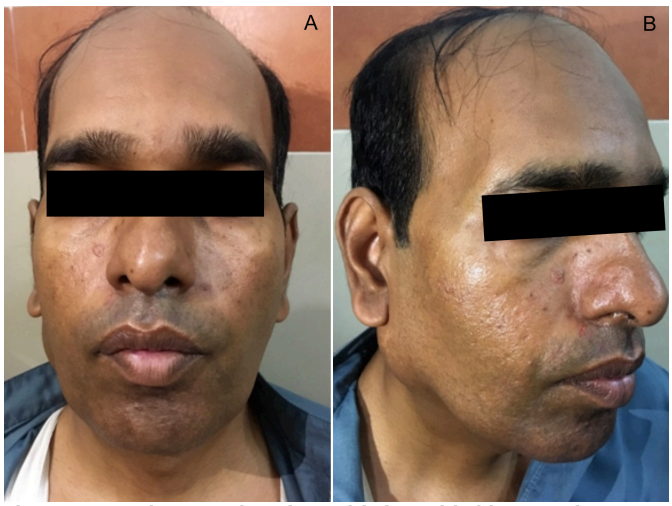

Figure 1, A and B: 'Hatchet' face with frontal baldness and temporo mandibular wasting, and right parotid swelling.

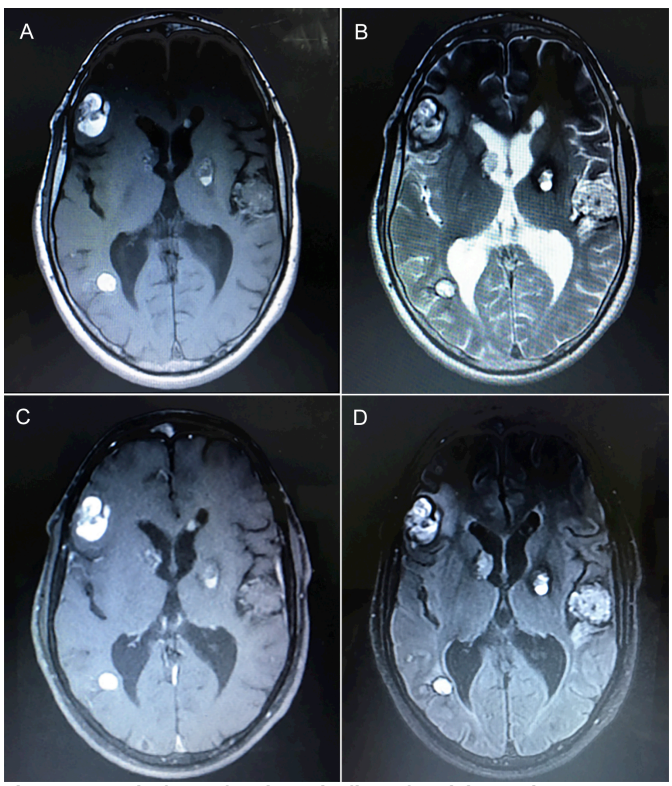

Figure 2, A and B (upper) and C and D (lower): Axial T1 and T2 MR Images (upper) and Gadolinium-enhanced and Fluid-attenuated inversion recovery (FLAIR) (lower) MR Images showing multiple characteristic 'popcorn-like' lesions called cerebral cavernous malformations.

Although genetic testing was not available, because of his typical progressive history of weakness and wasting of facial, bulbar and upper distal muscles with the presence of myotonia, history of similar complaints in his father, peculiar myotonic discharges on EMG and characteristic systemic involvement, the diagnosis of probable DM1 was made. Consultations from the cardiology, ophthalmology, endocrinology, and neurosurgery departments were sought, and anti-epileptic therapy for GTC seizures was initiated. Surgery was planned for the excision of parotid adenoma but the patient was lost to follow-up subsequently.

DISCUSSION

DM is the most common type of muscular dystrophy in adults. The core features in classic DM1 are distal muscle weakness leading to difficulty in performing tasks requiring fine dexterity of hands and foot drop; facial muscle weakness and wasting giving rise to ptosis and typical 'hatchet' face, and grip and percussion myotonia. However, myotonia affects other muscle groups as well including bulbar, tongue or facial muscles, causing problems with talking, chewing, and swallowing, as was evident by the history and examination in our patient.[1,2]

DM1 is characterised by the phenomenon of anticipation, in which the disease has an earlier onset and more severe course in the subsequent generations,[1] which was seen in our case too, as the patient's father had similar complaints for which he never sought medical advice. Moreover, he died of sudden cardiac arrest that was indicative of probable cardiac involvement, which is one of the manifestations of this disorder.[1,2] Cardiac involvement usually includes conduction abnormalities with arrhythmias and conduction blocks contributing significantly to the morbidity and mortality of the disorder. Posterior subcapsular cataracts, and minor cognitive and behavioural deficits are present in many patients. Though bilateral cataracts were present in or case but no intellectual or behavioural abnormalities were seen. Hypersomnia, nocturnal apnoeic spells and daytime sleepiness are common manifestations but were not reported by our patient. Gastrointestinal involvement includes nausea, vomiting, early satiety due to slow gastric emptying, irritable bowel syndrome, and symptomatic gallstones may be observed but these were not seen in our case. Endocrine abnormalities include testicular atrophy, hypogonadism, thyroid dysfunction and especially, insulin resistance leading to diabetes mellitus. Our patient was a known diabetic and childless that showed endocrinological manifestations of this disorder.[1,2]

Recent evidence has shown that DM1 patients are at an increased risk of certain cancers, most notably involving the thyroid, colon, testis, prostrate, ovary, endometrium, brain, and choroid.[3,4] Moreover, there is an elevated risk of benign tumours of thyroid, brain, colon, rectum, and uterus as well.[5] The risk of developing tumours in DM1 is more likely seen in the female gender.[6] There are a couple of case reports of DM1 associated with salivary gland neoplasms[7,8] but co-existence with multiple CCMs has not been reported so far in the literature. Our case of DM1 is unique as the presence of pleomorphic adenoma of the parotid gland in DM1 is itself a rarity and that too with the co-existing multiple CCMs, which is being reported for the first time. Several molecular mechanisms have been proposed for the increased risk of developing tumours including RNA-mediated alterations in oncogene expression, modification in the coding of proteins, and dysregulation of the Wnt/ β-catenin signalling pathways.[9] Therisk of developing brain cancer in DM1 is five fold higher than in the general population. The exact mechanism underlying this susceptibility is unknown, but it has been attributed to an alternative splicing defect within the pre-mRNA

of specific genes,[6] though this susceptibility has not yet been reported for benign tumours of the brain like CCMs.

There is currently no cure for this multisystem disorder but multidisciplinary management is likely to reduce significantly the morbidity and mortality of these patients. It includes rehabilitative measures, such as bracing, scooters, or wheelchairs; ophthalmological and endocrinological consultations for cataracts, infertility and diabetes mellitus, respectively, and cardiological consultation for conduction defects and heart blocks. These patients are also at risk for developing malignant hyperthermia during anaesthesia, so it has to be kept in mind while operating for the tumours. Anti-myotonia therapy such as phenytoin is helpful when muscle stiffness is frequent and persistent or if the pain is the prominent feature but caution is needed in DM patients with cardiac involvement.

Our case report is one of its kind as the presence of pleomorphic adenoma of the parotid gland in DM is itself a rarity and that too with the co-existing multiple CCMs, which is being reported for the first time. Molecular studies aiming at elucidating the biological pathways involved in DM-related tumour genesis are warranted.

PATIENT'S CONSENT:

Written informed consent was taken from the patient for the publication of this case report and accompanying images.

COMPETING INTEREST:

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

AUTHORS' CONTRIBUTION:

SI: Concept, acquisition, drafting, and integrity of the work.
MZS: Drafting and critical appraisal of the work.
All the authors have approved the final version of the manuscript to be published.

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