CHAPTER

87

Tough Calls in Neurology

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INTRODUCTION

Medicine is an ever changing science and more so are neurological sciences with breathtaking developments occurring on a day to day basis. Technological advances have helped us understand and diagnose diseases better. With the advent of various MRI techniques, neurology has received a face change. Newer diagnostic tests have come and helped us diagnose hitherto unknown diseases. Latest drugs have helped us control and cure neurological disorders. Immune-mediated disorders may be mentioned here as an example where new auto-antibodies are being recognized and newer drugs are controlling the disease without the side effects of steroids. Robotic tools have arrived to strengthen the surgeon's hands. Therapeutic nihilism is no longer warranted in neurology. However the challenges to the clinician are ever increasing. He cannot afford to have rigid ideas and risk missing treatable disorders. He should use all the diagnostic and treatment modalities in his armamentarium judiciously. To top it all, the possibility of getting entangled in legal battles looms large in the case of unhappy patients or relatives.

Each case is thus a challenge and the practicing neurologist would agree to at least one humbling experience daily. In other words each patient is a "tough call" unless proved otherwise. To showcase this we present some interesting clinical scenarios which include uncommon presentation of a common disease like Myasthenia Gravis, common presentation of an uncommon disease like Sjogren's syndrome, uncommon but dreaded complication of surgeries in prone position and treatable disorders masquerading as a degenerative disease like MND. These cases highlight the importance of careful and repeated clinical examinations and laboratory investigations before a definitive diagnosis is made.

CASE NO. 1

A 27-year-old female admitted with 20 days history of difficulty in swallowing, change in voice with diurnal variation and fatiguability. There was no history of diplopia, drooping of eyelids, difficulty in eye closure and facial weakness. On examination, patient showed tongue atrophy with fasciculation (Figure 1), minimal limb weakness and absent tendon reflexes. Fatiguability tests were positive. Repetitive nerve stimulation revealed decremental response. Computerized tomography (CT) scan of thorax showed thymic enlargement. Acetylcholine receptor (AChR) antibody was positive (11.3 nmol/lit). Anti-muscle-specific receptor tyrosine kinase (Anti-MuSK) antibody was negative. Patient progressed to respiratory distress within a day of admission required ventilatory support followed by tracheostomy. She was diagnosed as myasthenic crisis. As the patient was not affordable for plasmapheresis and intravenous immunoglobulin, Injection methylprednisolone was given and planned for thymectomy. Patient lost on follow-up.

After 3 months, patient presented again with bulbar weakness with minimal limb weakness. On examination, patient showed tongue atrophy with fasciculation. Patient progressed to respiratory failure and required ventilatory support. Plasmapheresis was given. On follow up after 4 weeks tongue fasciculation disappeared and tongue atrophy is improving (Figure 2).

Fig. 1: Showing tongue atrophy with fasciculation

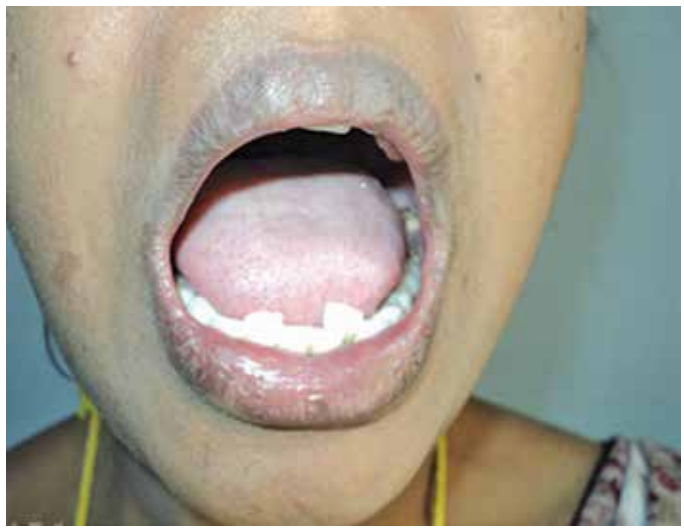

Fig. 2: Showing improvement in tongue atrophy

Fig. 3: Showing hyperpigmentation of cheek

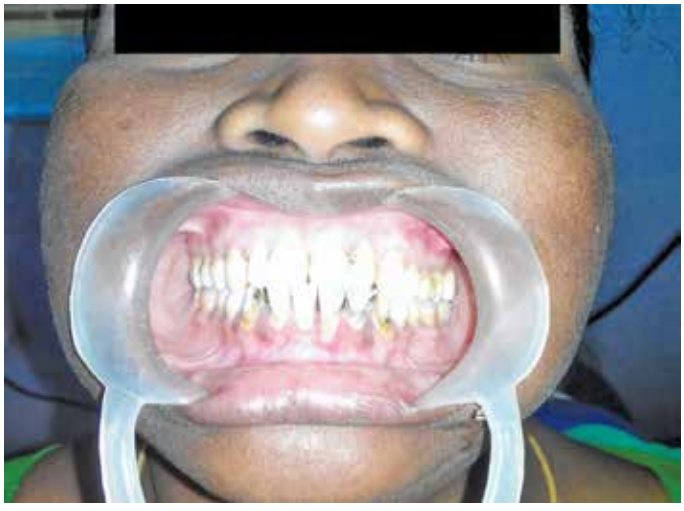

Fig. 4: Showing multiple dental caries

Discussion

Myasthenia Gravis (MG) is a reversible autoimmune neuromuscular junction disorder associated with diurnal variation, weakness and fatiguability of voluntary muscles. It commonly affects extraocular muscles first. Bulbar onset myasthenia gravis is relatively rare. Atrophy of muscles is a rare feature of MG. Variety of antibodies are involved in the pathogenesis of MG. Myasthenia Gravis (MG) is an autoimmune disease caused by binding of autoantibodies to receptors involved in neuromuscular transmission. About 80% of patients have detectable serum antibodies against AChR (AChR-Ab). Approximately 15-20% of MG patients do not have any detectable AChR-Ab. Of these patients antibodies against muscle specific tyrosine kinase (MuSK) are positive in 30-50%. 3 types of AChR antibodies are identified which includes acetylcholine binding, blocking and modulating antibodies.

Histological examination revealed myopathic changes [(mini-cores and ragged red fibres (mitochondrial aggregates)] were common in MuSK MG patients, whereas fibre type grouping (neurogenic finding) and atrophy were frequent in AChR MG patients[1]. The presence of fibre type grouping in AChR positive MG group might be explained by the blockage of AChR receptor binding that causes the internalization and degradation of AChR leading to denervation of affected muscle[2].

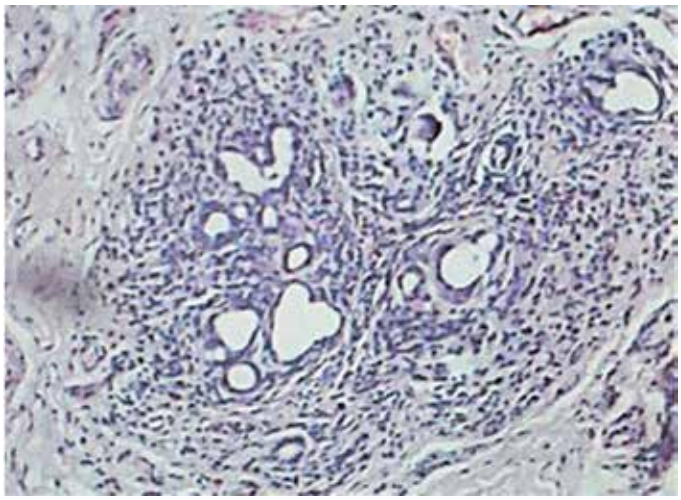

Fig. 5: Showing lymphocytic infiltrate in minor salivary gland and atrophy of acinar cells

In our present case, patient had bulbar onset MG which progressed to myasthenic crisis. Patient was treated with plasmapheresis and steroids after which she recovered. The unusual finding in this case was tongue atrophy with fasciculation which improved with plasmapheresis.

Cranial and bulbar muscle weakness with atrophy including tongue is more common in anti-MuSK MG[3,4]. Tongue atrophy is a rare feature of AChR antibody positive MG[5]. The exact pathogenesis of tongue atrophy is not known.

Conclusion

Bulbar onset MG is relatively rare. Tongue atrophy with fasciculation has been reported in anti-MuSK myasthenia gravis but rare in AChR antibody positive MG. This case highlights AChR antibody positive bulbar onset MG with tongue atrophy and fasciculation and improvement following plasmapheresis. Physician may be easily misled to think about motor neuron disease in the above case.

CASE NO. 2

A 38 year old previously healthy female was admitted with sudden onset severe weakness of all 4 limbs and neck with dyspnea at rest. She gave a history of analgesic intake prior to the illness for dental caries. She had no other systemic illness in the past except for recurrent renal calculi. On examination she was conscious,tachypneic with respiratory rate of 40/minute. Hyperpigmentation of both cheeks were noted (Figure 3). Multiple dental caries were also noted (Figure 4). The blood pressure was 120/70 mm Hg, pulse rate was 84/min with no pallor, icterus, cyanosis, clubbing, oedema or lymphadenopathy. Neurological examination revealed severe flaccid weakness of all the 4 limbs and involving

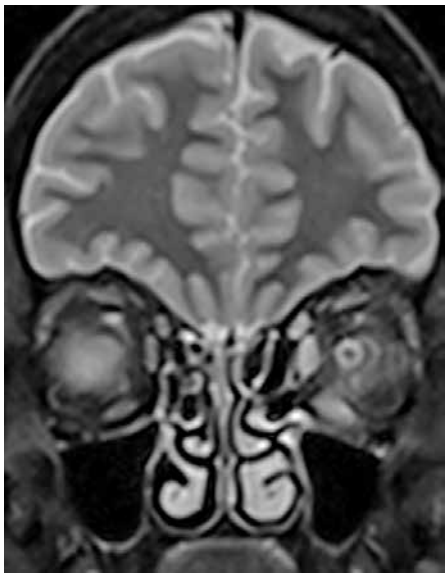

Fig. 6: Magnetic Resonance Imaging shows enlarged hyper intense extra ocular muscles [left superior rectus, inferior rectus and medial rectus]

neck flexors with diminished deep tendon reflexes, absent plantar reflexes without any cranial nerve or sensory involvement. Other systems were normal. ECG showed Prominent U waves, ST depression and Prolonged QTc interval. Blood counts were within normal limits. Blood Urea and Creatinine values were 30 mg/dl and 1.1mg/dl respectively. Severe hypokalemia was noted (serum K+ 1.4mEq/L). Serum sodium was 148.4mEq/L,Bicarbonate was 6.8 mEq/L. ABG revealed metabolic acidosis with compensatory respiratory alkalosis. Diagnosis of distal renal tubular acidosis leading to hypokalemic paralysis with impending respiratory failure was made and managed with potassium replacement and acetazolamide. Patient improved dramatically. Owing to the presence of metabolic acidosis with hypokalemia, nephrocalcinosis and dental caries, the possibility of sjogrensyndrome was considered which was later confirmed by a 3+ positive Anti nuclear antibody showing a nucleoplasm coarse granular pattern. Anti Ro levels were 97 U/ml. Lip biopsy was taken which showed lymphocytic infiltrate in minor salivary gland and atrophy of acinar cells (Figure 5) thereby confirming the diagnosis of sjogren syndrome. Patient is on low dose prednisolone and on regular follow up.

The important differential diagnosis of acute areflexic quadriparesis includes Guillaine Barre syndrome, hypokalemic paralysis, transverese myelitis and multiple sclerosis. Sjogren syndrome is a chronic autoimmune disease characterised by progressive lymphocytic infiltration of exocrine glands with varying degrees of systemic involvement.[6] Sjogren syndrome presenting as hypokalemic periodic paralysis caused by distal RTA have been rarely reported.[7] The spectrum of renal disease includes interstitial nephritis, which can manifest as distal RTA, proximal RTA, tubular proteinuria, nephrogenic diabetes insipidus, glomerular diseases, or renal failure. The most common manifestations are related to tubular dysfunction which results from chronic interstitial nephritis.[8] The most common presenting symptoms of sjogren syndrome are dryness of mouth and eyes. The most common extra glandular manifestation of sjogren syndrome includes Arthralgia (60%), Raynauds henomenon (37%), lymphadenopathy (14%), Pulmonary involvement (14%), vasculitis (11%) and renal involvement (9%) respectively. This serves to highlight the fact that patients presenting with hypokalemic paralysis with metabolic acidosis can be due to Sjogren syndrome which needs to be investigated and treated appropriately to avoid future recurrences.

CASE NO. 3

40 Year old man, non diabetic, not obese, underwent lumbar disc surgery under general anaesthesia in the prone position. In the recovery room, he noticed painless loss of vision in the left eye. 24 hours later neurologist was called to evaluate the cause. Examination of the left eye revealed, no light perception with relative afferent pupillary defect and restriction of extra ocular eye movements. Fundus examination showed normal disc and vessels right side. On affected side, the disc was pale and there was no CRA or CRV occlusion. Ocular tonometry showed intraocular pressure of 18mm Hg. Magnetic Resonance Imaging showed enlarged hyper intense extra ocular muscles[left superior rectus, inferior rectus and medial rectus] (Figure 6). Magnetic Resonance Imaging of Brain did not show any abnormalities in optic nerves, occipital lobes and rest of the visual pathways and cavernous sinus. Blood investigations including blood biochemistry were normal. Diagnosis of ischemic orbital compartment syndrome was made. High dose IV methylprednisolone [1gm] was started. Canthotomy and cantholysis was performed but no improvement in visual acuity or ocular movements.

Discussion

Perioperative ischemic optic neuropathy[ION] is a rare, unexpected and devastating complication occurring overall 1 in 60,000 to 1 in 1,25,000 anaesthetics. Ischemic optic neuropathy[ION] following spinal surgery forms the highest frequency (0.03 percent)[9,10]. In the above case, patient presented with ischemic orbital compartment syndrome following spinal surgery done in the prone position. Ischemic ocular compartment syndrome is an acute opthalmological emergency requiring prompt decompression to relieve the increased intraocular pressure. It is reported in spine surgery done in prone position. The possible mechanism is the progressive orbital edema secondary to prone position and possible unilateral direct pressure from the headrest device on periorbital structures, resulting in congestion at the orbital apex, with a subsequent compartment syndrome and ischemic orbit.[11] The prolonged operation was also a significant factor in the irreversible ischemia and poor overall visual and functional prognosis.

Ophthalmologists, as well as neurosurgeons and anaesthesiologists, should be familiar with this rare complication and the mechanism of visual loss in patients

Fig. 7: Showing left lateral rectus palsy

Fig. 8: Showing wasting and weakness of tongue on both sides

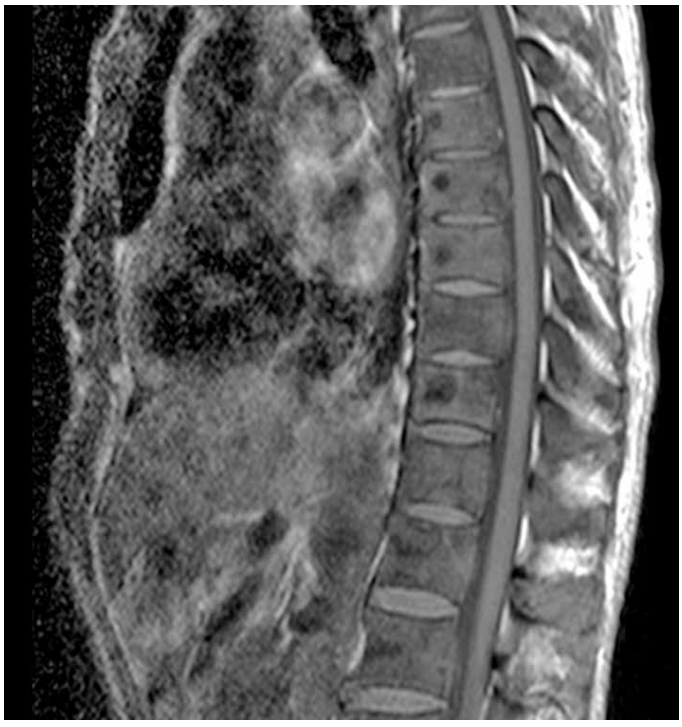

Fig. 9: MRI (T1Sagittal) Dorsal spine showing multiple well defined hypointense sclerotic secondaries

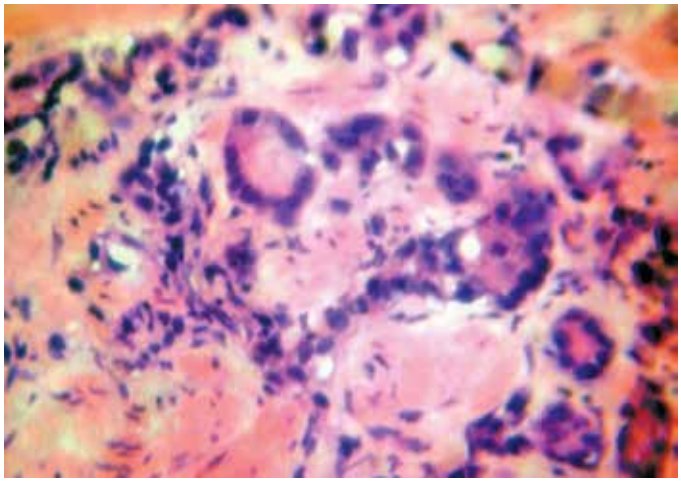

Fig. 10: HPE of prostatic Biopsy specimen showing irregular small round to oval glands lined by columnar cells with mild to moderate nuclear pleomorphism and hyperchromatism.Sheets of tumour cells with diffuse infiltration of stroma suggestive of grade 2 adenocarcinoma of prostate

undergoing prolonged surgery in prone position. . High risk patients are defined as those who undergo spine procedures while positioned prone and who have prolonged procedures, experience substantial blood loss, or both[12]. It is essential to monitor these patients during and after surgery and to intervene surgically once the diagnosis of ischemic orbital compartment syndrome is made although the prognosis is poor.

CASE NO. 4

65 year old male, non smoker, non alcoholic, not a known diabetic or hypertensive presented to us with dysphagia with nasal regurgitation, difficulty in marshaling the food and double vision on looking distant objects of 1 month duration. On examination, the patient was conscious, oriented, afebrile, cervical lymph node enlargement, left lateral rectus palsy was present (Figure 7). Pupil 3mm equally reacting to light on both sides. Fundus examination was normal. Left gag reflex was sluggish. Tongue wasting and weakness was noted on both sides (Figure 8). Left 6^{th}, left 10^{th} and bilateral 12^{th} cranial nerves were involved. Patient did not have florid meningeal signs. There was no limb weakness. All deep tendon jerks were normal. Plantars were flexor. Sensory and cerebellar systems were normal. On rectal examination, hard prostatic mass was felt.

Blood investigations including blood biochemistry were

normal. Vasculitic profile including ANA were normal. X Ray chest PA view was normal. ENT opinion revealed no lesion in nasopharynx. Ultrasonogram of abdomen and pelvis showed enlargement of prostatic gland (4.6X4.7cm). Serum prostatic specific antigen was more than 1000ng/ml. MRI Brain(plain and contrast) was normal. MRI (T1Sagittal) Dorsal spine showed multiple well defined hypointense sclerotic secondaries (Figure 9). Fine needle aspiration cytology (FNAC) of left cervical lymph node showed metastatic deposits. Histopathological Examination(HPE) of prostatic gland biopsy showed irregular small round to oval glands lined by columnar cells with mild to moderate nuclear pleomorphism and hyperchromatism. There are other foci showing sheets of tumour cells with diffuse infiltration of stroma. These features were suggestive of grade 2 adenocarcinoma of prostate (Figure 10). CSF analysis showed 40 cells/cu mm which were predominantly mononuclear cells with mildly elevated protein. CSF sugar was low at 20mg percent. Diagnosis of leptomeningeal metastasis (multiple cranial nerve palsies) due to carcinoma prostate was made based on the hypercellularity, elevated protein and hypoglycorrhachia of the CSF. Patient was subjected to orchidectomy and planned for radiotherapy and antiandrogen therapy. Patient is on follow up.

Discussion

Metastatic prostatic carcinoma commonly involves bones and extra pelvic lymph nodes. CNS involvement is unusual and particularly the occurence of leptomeningeal metastasis is extremely rare , with few cases described in the literature[13]. The reported incidence at autopsy vary from 0.6 to 4.4 percent[14]. Brain metastasis occurs in 25 percent of patients with malignancies and 50 percent of neoplasms in the brain are metastatic[15]. The most common sources of metastasis to the brain are carcinoma lung, breast, kidney and melanoma.[16,17] The most common sites of prostate cancer metastasis include the bone, lung and liver[18]. Brain metastasis is very rare in prostate cancer. The intracranial sites of prostate cancer metastasis are the leptomeninges, cerebrum, and cerebellum[19]. On the other hand, the diagnosis of metastatic prostate carcinoma to the brain has rarely been made in living patients. Brain metastasis in prostate cancer occurs late in the course of the disease. It usually represents the failure of hormone-deprivation therapy and the presence of disseminated disease. The long time between diagnosis and brain involvement strongly favors the cascade theory of tumor spread [20;21]. Metastasis to the brain can occur by way of Batson's plexus or by direct extension from adjacent structures such as the sphenoid bone or sinuses. Other primary cancers, such as lung and breast tumors, are more likely to have intraparenchymal metastases than leptomeningeal involvement. Patients rarely present with neurologic symptoms as the first manifestation of prostate cancer. Presentation with a solitary brain metastasis as the only site of prostate cancer spread is even rarer. Leptomeningeal metastasis is usually clinically silent, although it can present with deficits in multiple anatomic sites[22]. Gadolinium-enhanced MRI is required to exclude or confirm the presence of brain metastases. A two-week course of radiotherapy is the most common treatment for patients with multiple brain metastases or leptomeningeal involvement. Brain metastasis is associated with a poor prognosis. Once prostate cancer has spread to the brain, the one-year survival rate is 18 percent, with an average survival of 7.6 months.

Our patient presented with multiple cranial nerve palsies. The FNAC of the cervical lymphnode gave clue as metastatic lesion. Inspite of extensive metastasis, there is no evidence of cord compression. CSF analysis showed 40 cells/cumm which were predominantly mononuclear cells with elevated protein. CSF sugar was low at 20mg percent.

The diagnosis of leptomeningeal metastasis (multiple cranial nerve palsies) due to carcinoma prostate was made based on the hypercellularity, elevated protein and hypoglycorrhachia of the CSF as per category3 in the National Comprehensive Cancer Network (NCCN) guidelines[23]. This is the most plausible explanation for cranial nerve involvement in this case. Our emphasis is however on the protean clinical presentations of carcinoma prostate with no clues to the primary site of involvement. A high index of suspicion is needed when an elderly male approaches us with such a clinical presentation.

CONCLUSION

In case no.1, a young lady presented with short duration of recurrent bulbar symptoms. We looked for antibodies to MG and found to be positive. The general teaching is that muscle atrophy is not a feature of MG and is a feature of anterior horn cell disease. It still holds good. It is a typical example of MG masquerading as MND. An interesting feature is reversal of tongue atrophy following immunotherapy (plasmapheresis).

Steroids are not useful in GBS. However, in the second case, it proved to be the lifesaving drug since sjogren syndrome was identified as the cause for the clinical presentation of acute flaccid paralysis.

Anything can happen in medicine. Surgeries done under prone position is commonly done procedures in neurosurgery and orthopedic surgeries. Nobody would have anticipated this catastrophic complication in this third case.

In case no.4, the diagnosis of MND is considered a death sentence due to lack of treatment and the mortality associated with it. It is important to consider MND mimics which could be treatable and may not carry a grave prognosis. Secondary causes should be considered and looked for while dealing with a clinical presentation mimicking MND. In this case, extra ocular muscle involvement (lateral rectus) is the catch point. The subtle CN palsy and careful examination of cervical lymphnode lead us to a treatable malignant disease presenting like MND.

Thus all the four cases are examples of tough calls in neurology.

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