Polyneuritis Cranialis in Covid-19

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Abstract
The global pandemic CoVID – 19 has affected several people around the world for about a year
now. The exact mechanism of CoVID – 19 induced neurological symptoms is still unclear.
Complex mechanism of the diverse tactics of CoVID – 19 affecting the brain stem nuclei
remains uncertain.
However, Early and late neurological manifestation of CoVID – 19, ranging from catastrophic
encephalitis to subtle manifestation like ageusia and anosmia have been well reported. Atypical
neurological presentations like acute hearing loss, speech impairments and dysphagia are still not
well known.

Keywords: Multiple Cranial Neuropathy, Immune mediated, Speech-Hearing-Dysphagia, CoVID-19

Introduction:
Coronavirus infectious disease 2019 has spread around various parts of the world and was
declared a global pandemic. There have been several reports of cases with widespread disease
presentation ranging from respiratory symptoms, kidney injury, sepsis, encephalitis to brain
strokes7,11. Since the incept of CoVID – 19, focus has been on deriving the pathophysiology of
infestation, the resulting illness and extent, to manage the pandemic well. Common symptom of
anosmia and ageusia with CoVID – 198,13 and the probability of direct injury to the olfactory and
gustatory receptors were reported. Isolated facial diplegia10, cranial neuropathies5 associated with
CoVID – 19 as a possible auto immune mediated disorder was postulated. More commonly
AIDP, AMSAN with few GBS/Miller-fishers overlap variants have been reported1. In this paper,
we describe Para and post infectious multiple cranial neuropathies in CoVID-19.
Case History:
Four cases with clinical presentation of acute onset facial weakness, hearing loss, slurring of speech, difficulty swallowing was evaluated for CoVID – 19.

Case 1: 49-year-old gentleman complained of jaw stiffness and swallowing difficulty for 3 days. History of intermittent fever, loss of taste and smell of two-day onset with multiple systemic comorbidities. RT-PCR for SARS CoV-2 was positive with CT Chest scores of 5/25.

Haemodynamically stable, anosmia, restricted jaw opening, ageusia, Bi-facial LMN weakness, left HB Gr. IV > Right HB Gr III, diminished gag, Symmetrical velum and tongue. Normal motor-sensory examination and cerebellar findings. Labial distortions, perceptually normal voice with intelligible speech. Oral phase dysphagia with safe swallow on bedside swallow evaluation (BSE). Rehabilitation focused on motor speech training, biofeedback, incentive spirometry and deep breathing exercises.

Case 2: 65-year-old gentleman with complaints of confusion, forgetfulness, slurring of speech, sudden worsening of hearing (Left> Right) with speech understanding difficulty, dizziness, imbalance of one-week onset with multiple systemic comorbidities. No history of fever, breathing difficulty. Prior history of bilateral moderate SNHL (evaluated before 4 months). RT PCR for SARS CoV – 2 was positive with CT chest scores of 8/25.

Conscious, oriented, SpO2 – 92%, Postural hypotension between supine and standing with diastolic difference of 16 mm Hg, systolic difference of 26 mm Hg. Single breath count < 8. Bi facial LMN weakness Left HB Gr III > Right HB Gr II. Preserved gag, symmetrical velum, tongue. Preserved motor-sensory function with truncal and appendicular ataxia. Mild Dysarthria, slightly increased effort with distortion of lingual sounds, perceptually normal voice. BSE indicated oral phase dysphagia with safe swallowing. Impaired recent memory - MMSE 20/30, MOCA 16/30. Evaluation (Table 1) indicated worsened SNHL with very poor speech discrimination scores (Left>Right), Bilateral Outer Hair Cell Dysfunction. Auditory brainstem responses (ABR) indicated delayed absolute latencies of Peak III &V, prolonged inter-peak latencies (Table 2) with bilateral vestibulo-collic reflex pathway dysfunction. Speech rehabilitation focused on motor speech training, incentive spirometry and deep breathing exercises.

Case 3: 48-year-old gentleman with one-week onset progressive hearing loss and tinnitus in both ears, slurring of speech, facial weakness, difficulty swallowing and imbalance. He was positive for SARS CoV – 2 and treated one month prior. History of haemodialysis (HD) five times in a span of eight days for azotaemia with uremic symptoms at an outside facility, three weeks ago. Repeat RT PCR for SARS CoV – 2 was negative with CT Chest not indicative of pneumonia. SARS CoV – 2 Antibody (Total & IgG) was positive.

Vitals stable, bifacial LMN weakness Left HB Gr IV > Right HB Gr III. Difficulty in alternating jaw movements, poor lip seal, preserved sensation. Symmetrical velum elevation, preserved gag. Restricted tongue range and speed of motion. Normal motor-sensory functions with truncal
ataxia. Mild dysarthria with increased effort in speaking with distortions for labial plosives. BSE indicated oral phase dysphagia with safe swallow. Audiological evaluations (Table 1) indicated bilateral SNHL, poor speech discrimination scores, bilateral outer hair cell dysfunction, prolonged absolute latencies and inter-peak latencies of ABR with poor morphology (Table 2) and bilateral vestibulo-collic reflex pathway dysfunction. Rehabilitation focused on motor speech training.

**Case 4:** 51-year-old lady with history of difficulty chewing solids for 1 month, sensation of food stuck in throat. Nasal twang in voice noticed for about two weeks. Ptosis of left eyelid, coughing and choking on liquids gradually progressing one-week duration. One-month prior she had fever and cough. No appropriate medical attention was sought due to inadequate facilities in the village. RT PCR for SARS CoV – 2 was negative. CT Chest not indicative of pneumonia. SARS CoV – 2 Antibody (Total & IgG) was positive.

Vitals stable, reduced jaw opening, bi-facial weakness, left HB Gr III > right HB Gr II, diminished gag – sensation preserved, reduced velar elevation, normal tongue functions. Intelligible speech with hypernasality and nasal murmur. Normal motor-sensory with normal cerebellar examination. BSE indicated, anterior spillage on the left > right, increased effort in swallowing, delayed cough after swallow. Video-Laryngoscopy was normal. Mild Oro - Pharyngeal dysphagia with Velopharyngeal incompetency, nasal regurgitation, prolonged pharyngeal transit, vallecula and pharyngeal residue with no gross or silent aspiration noted on Video-fluoroscopic swallow evaluation (VFSE). Rehabilitation focused on pharyngeal strengthening exercises, swallow manoeuvres, oro-motor exercises.

**Discussion:**
Normal MRI findings, Normal upper and lower limb with prolonged latencies, reduced amplitude in facial Nerve conduction study (NCS), negative viral markers and Antiganglioside antibodies, absence of viral RNA and Albumin cytological dissociation in CSF was seen in all four cases.

Case 1 and 2 had elevated CSF Interleukin - 6 (IL-6) levels, 24 pg/mL and 37 pg/mL respectively.

Cases – 1, 2, 4 had immediate clinical improvement with pulse dose methylprednisolone and anti-viral with supportive medications during their stay.

Case – 3 received plasma exchange (5 cycles) and IV corticosteroids.

All the four cases were serially followed up after 15 days of discharge.

Case – 1 had involvement of cranial nerves I, V (motor) VII & IX. On follow up, mild residual facial weakness - left HB Gr II was noted.
Case – 2 had Bilateral Cranial Nerve VII (Motor), VIII, XII impairments, autonomic neuropathy. On follow up, dysautonomia resolved, facial weakness improved – left HB Gr II. Improved hearing levels and speech discrimination scores (Table 1 & 2), mild gait ataxia persisted.

Case – 3 had a Para-infectious Acute Kidney Injury treated with HD subsequently followed by post infectious bilateral Cranial Nerves V (Motor), VII (Motor), VIII & XII impairments. On follow up, facial weakness improved to Left HB Gr II, mild gait ataxia persisted. He was able to walk without support. Dysarthria resolved; hearing abilities improved to normal levels (Table 1 & 2).

Case – 4 had bilateral cranial nerves V, VII, IX (Motor) & X involvement. Absent ipsi R1 bilaterally, with preserved bilateral ipsi and contra R2 indicated bilateral involvement of trigeminal nuclei on Blink reflex test. On follow up, good clinical improvement in her swallowing and residual facial weakness – Left HB Gr II was noted.

We propose that the pathophysiology of brainstem invasion for the cases described above could fall in any of the following three mechanisms.

1. **Direct viral invasion**
   Brainstem nuclei being the potential target of CoV-2 due to high expression of angiotensin converting enzyme - 2 (ACE-2)\(^2\), the entry of virus into the CNS is via the olfactory nerve and bulb followed by trans-neuronal spread causing brainstem dysfunction and neuronal death\(^4\). The first central relay for olfaction and deglutition, the nucleus of solitary tract (NTS) also integrates information from Cranial Nerves V, VII, IX & X\(^1\). Direct viral invasion of NTS, medullary – thalamocortical networks may range from gustatory dysfunction to facial-bulbar weaknesses\(^9\). Presence of viral RNA in CSF ascertains the possibility of direct viral invasion into the nerve roots\(^1\). However, onset of symptoms, time-course of evaluation and yield of viral isolations in CSF may be influential on this.

2. **Brainstem inflammatory responses**
   The virus enters through olfactory, trigeminal nerves, and further propagates via microglial cells and nerve sheath, as noted in primates. Brainstem nuclei invasion evokes strong neuro-inflammatory responses by microglial activation. Neuro-inflammatory damage and injury to the brainstem nuclei can lead to demyelination or poly-cranial neuropathy with or without long tract signs. Elevated Proinflammatory cytokines (IL-6 > 7pg/mL & IL-1β > 2.56 pg/mL) levels in CSF can serve as a biochemical marker for brainstem inflammation\(^3\).

3. **Auto Antibodies mediated immune disorder**
   The role of gangliosides in driving peripheral nerve autoimmunity in CoVID – 19 is supported by evidence that describes involvement of glycoproteins along with spike S protein in binding the virus to host ACE2 receptors\(^7\). Possibility of cross reactivity between epitopes with spike bearing gangliosides and neuro-glycolipids leading to molecular mimicry existing between other
neurotropic viruses cannot be excluded⁵. The anti-gangliosides antibodies may be negative in such cases due to involvement of different immune-mediated mechanisms which are still not well understood¹.

We have highlighted the unusual presentation in the form of restricted jaw movements, altered speech, hearing loss and dysphagia. Preserved reflexes, multiple cranial nerve involvement, negative antibody profile as a differential to MFS, a rare variant of GBS. Response to immune therapy supports immune mediated disorder associated with CoVID – 19 as the pathophysiology in the cases above.

Polyneuritis cranialis is also known as the oculo-pharyngeal subtype of GBS. However, none of our cases had ocular involvement. Importantly the involvement of cranial nerves VIII, IX, X & XII have not been reported earlier associated with CoVID – 19. This sub group can be termed as CoVID – Polyneuritis cranialis syndrome due to its atypical nature. Nevertheless, this needs further validation with large samples.

Early initiation of Immuno-therapy should be considered when clinically indicated helping in ameliorating cytokine effects, immune molecule associated damage and complete restoration of neurological status.

A potential high risk of progressive cell death, demyelination due to intense immune response, inflammatory molecular release is expected in this population¹². Identifying brainstem inflammatory processes using invasive methods such as CSF cytokine levels may be challenging in critically ill patients with CoVID – 19. Auditory Brainstem Responses (ABR) can serve as a simple, non-invasive modality to evaluate and monitor acute and chronic sequelae of brainstem involvement¹². Periodic evaluations (baseline, 1 month, followed by 3 months interval) can be useful in post-infectious immune mediated brainstem dysfunctions as described in cases 2 and 3 in the form of prolonged absolute and inter-peak latencies in ABR and poor speech discrimination scores. ABR serves as a reliable, objective measure of integrity of brainstem auditory pathway. When combined with other audiological tests can be highly informative to understand the impact of CoVID – 19 on auditory processing. At the time of writing this paper, no documents of audiological profile in CoVID – 19 cases have been reported earlier.

As we move to an era post-CoVID – 19 and vaccine development, from the current scenario we can assume a surge in post infectious auto immune pathologies. Our preparedness to identify and handle acute auto immune reactions and chronic auto immune pathologies on inoculation may be the need of the hour. The extent of molecular mimicry between human proteome and SARS CoV – 2 needs careful analysis during development of vaccines⁶. Identifying the biochemical markers, epitopes specific to SARS CoV-2 becomes necessary.

**Conclusion:**

An understanding of neurological impairments secondary to CoVID – 19 requires careful examination, followed by multidisciplinary evaluations, non-invasive and reliable measures that
contribute to understanding the nature of the disease. Clinicians need to incorporate methods that add value to making diagnosis and initiation of appropriate pharmacological and rehabilitation therapies at the earliest. Periodic follow up of this group is needed to understand the chronic effects of the disease.
Table – 1. Case 1 & Case 3 Audiological findings summary

<table>
<thead>
<tr>
<th>CASES</th>
<th>Pure Tone Audiometry</th>
<th>Speech Audiometry</th>
<th>Tympanometry</th>
<th>Reflexometry</th>
<th>OAE</th>
<th>c - VEMP</th>
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<td>CASE 2</td>
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<td>Right: 57 dB HL Moderate SNHL</td>
<td>Left: 67 dB HL Moderate SNHL</td>
<td>SRT: Right: 80 dB HL Left: 90 dB HL</td>
<td>SDS: Right: 50% Left: 20%</td>
<td>Bilateral ‘A’ type – Normal compliance and peak pressure</td>
<td>Absent Ipsi – Contra reflexes</td>
<td>Bilateral Absent DPOAE</td>
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<td>21 days after discharge</td>
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<tr>
<td>Right: 45 dB HL Moderate SNHL</td>
<td>Left: 60 dB HL Moderate SNHL</td>
<td>SRT: Right: 55 dB HL Left:70 dB HL</td>
<td>SDS: Right: 95% Left: 80%</td>
<td>Bilateral ‘A’ type – Normal compliance and peak pressure</td>
<td>Absent Ipsi – Contra reflexes</td>
<td>Bilateral Absent DPOAE</td>
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<td>CASE 3</td>
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<td>Right: 52 dB HL Moderate SNHL</td>
<td>Left: 48 dB HL Moderate SNHL</td>
<td>SRT: Right: 75 dB HL Left: 80 dB HL</td>
<td>SDS: Right: 95% Left: 30%</td>
<td>Bilateral ‘A’ type – Normal compliance and peak pressure</td>
<td>Absent Ipsi – Contra reflexes</td>
<td>Bilateral Absent DPOAE</td>
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<td>21 Days after Discharge</td>
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<tr>
<td>Right: 25 dB HL, PTA1 – 41 dB HL Moderate HF Sloping SNHL</td>
<td>Left: 20 dB HL PTA1 – 35 dB HL Mild HF Sloping SNHL</td>
<td>SRT: Right: 35 dB HL Left: 30 dB HL</td>
<td>SDS: Right: 95% Left: 100%</td>
<td>Bilateral ‘A’ type - Normal compliance &amp; Peak Pressure</td>
<td>Bilateral Ipsi – Contra reflexes present at normal levels except at 4KHz</td>
<td>Bilateral DPOAE seen till Fdp – 1003 Hz</td>
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Table – 2. Cases 1 & 3 Brainstem Evoked Response Audiometry (BERA) Findings during Admission & 3 weeks after discharge

<table>
<thead>
<tr>
<th>Case 2</th>
<th>Case 3</th>
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<tr>
<td>BERΛ @ 90 dB nHL for Click stimuli</td>
<td></td>
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<tr>
<td>Right Ear</td>
<td>Left Ear</td>
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<tr>
<td>III msec (mV)</td>
<td>III msec (mV)</td>
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<tr>
<td>Low Rate 11.1/s</td>
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<tr>
<td>4.42 (0.11)</td>
<td>6.47 (0.23)</td>
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<tr>
<td>High Rate 91.1/s</td>
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<tr>
<td>4.65 (0.07)</td>
<td>6.96 (0.19)</td>
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<tr>
<td>During Admission</td>
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<tr>
<td>Low Rate 11.1/s</td>
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<td>3.93 (0.14)</td>
<td>5.97 (0.38)</td>
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<td>21 days after discharge</td>
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<tr>
<td>Low Rate 11.1/s</td>
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<tr>
<td>4.12 (0.08)</td>
<td>6.19 (0.30)</td>
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<tr>
<td>High Rate 91.1/s</td>
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<tr>
<td>5.40 (0.08)</td>
<td>7.35 (0.24)</td>
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References: