CASE REPORT

Polyneuritis cranialis in covid-19

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ABSTRACT

Though the global pandemic Covid-19 has been around for a year, an understanding of the exact mechanism of Covid-induced neurological symptoms is still in its infancy. Understanding of the diverse tactics of Covid-19 affecting the brain stem nuclei remains unclear. 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 presentation like acute hearing loss, ataxia and dysphagia are still not well known.

Key Words: *Covid 19; Neuro inflammatory; Auto immune; Speech hearing dysphagia*

INTRODUCTION

Several researchers have discussed the commonly seen symptom of anosmia and ageusia with Covid 19, and the probability of direct injury to the olfactory and gustatory receptors. In the cases described, we have highlighted the involvement of other uncommonly reported lower cranial nerve impairments, which manifested in the form of facial weakness, altered speech, hearing loss and dysphagia. Cases of isolated facial diplegia, cranial neuropathies have been reported earlier associated with Covid 19 as a possible atypical auto immune response. More commonly AIDP, AMSAN with few GBS/Miller-fishers overlap variants have been reported. The atypical nature and broad spectrum of deficits manifested is not well understood. This calls for identifying the epitopes, moiety specific to SARS CoV-2 necessary.

CASE PRESENTATION

Case: 1

49-year-old gentleman reported with complaints of tightness of jaw, numbness of tongue and inability to swallow for 3 days. He had a history of intermittent fever, altered taste and smell of two-day onset with history of diabetes mellitus, systemic hypertension and dyslipidaemia [1]. Nested real time RT-PCR throat/nasopharyngeal swab for SARS CoV-2 were negative, while CT chest had typical patterns seen in COVID 19 pneumonia with a score of 5/25. Haemodynamically stable, normal vitals, SpO_2 >95% on room air, single breath count of 15. Bi-facial LMN weakness, left HB Gr.IV > Right HB Gr III, restricted jaw movements, diminished gag, normal motor, sensory examination and cerebellar findings.

3-tesla MRI Brain with contrast was normal. Deviated lip, symmetrical tongue with slow alternating movements. Symmetrical velum elevation. Normal perceptual voice rating, strong volitional cough. Labial distortions with normal speech fluency and prosody. Bedside swallow evaluation denoted mild anterior spillage, increased effort in swallowing, with palpable adequate laryngeal elevation, no noticeable signs of aspiration after swallow. Speech and swallow rehabilitation with non-speech isometric and isotonic exercises, in speech with articulatory drill and bio feedback, incentive spirometry and deep breathing exercises was initiated. Normal upper and lower limb nerve conduction study. CSF showed albumin cytological dissociation. Anti-ganglioside antibodies were negative [2]. He was treated with antiviral, antibiotics, bronchodilators, corticosteroids. On 3rd week follow up, he showed remarkable improvement in his oral motor functions, speech and swallowing. Mild residual facial weakness was noted on the left HB Gr.III [3].

Case: 2

65-year-old gentleman reported with complaints of confusion, forgetfulness, slurring of speech, altered taste sensation in form of bitter taste, sudden worsening of hearing (Left>Right) with severe difficulty in understanding speech, dizziness, imbalance of 1-week onset with no history of fever, breathing difficulty. Known diabetes mellitus and systemic hypertension. Prior history of bilateral moderate SNHL (evaluated before 4 months). Nested real time RT PCR throat/Nasopharyngeal swab for SARS CoV–2 was positive and CT chest had typical patterns seen in COVID 19 Pneumonia with a score of 8/25. On arrival, conscious, oriented, HR–80, SpO_2–92%, significant difference in systolic and diastolic BP between supine and standing with diastolic difference of 16 mm Hg, systolic difference of 26 mm Hg. Single breath count was less than 8. Preserved motor-sensory function with truncal and appendicular ataxia, impaired recent memory MMSE 20/30, MOCA 16/30 bilateral LMN facial weakness Left HB Gr III>Right HB Gr II. Symmetrical velum elevation, preserved gag. Mild dysarthria, slightly increased effort with distortion of lingual sounds in connected speech. Normal Perceptual voice rating, fair volitional cough. Bedside swallow evaluation indicated safe swallowing. 3-tesla MRI brain with contrast and MRA was normal. Normal upper and lower limb Nerve conduction study. Audiological findings indicated worsened hearing loss of sensory-neural type (Left>Right) with very poor speech discrimination (Left>Right), bilateral outer hair cell dysfunction. BERA indicated delayed absolute latency of Peak III and V, prolonged interpeak latencies, bilateral vestibulo-collic reflex pathway dysfunction. CSF study showed albumin-cytological dissociation. Anti-ganglioside antibodies were negative. Speech rehabilitation was initiated focusing on motor speech training along with Incentive spirometry and deep breathing exercises. He was initiated on antibiotics, broad spectrum antiviral, cortico-steroids and other supportive medications. Follow up after 21 days of discharge, his facial weakness (Left HB Gr II) and speech had improved to near normal functions. His Hearing abilities had improved slightly with good improvement in speech discrimination scores (Tables 1 and 2). Mild gait ataxia persisted.

Case: 3

48-year-old gentleman presented with complaints of one-week onset hearing loss, tinnitus in both ears, slurring of speech, facial weakness, difficulty swallowing and difficulty in walking, imbalance. No prior history of hearing loss. History of haemodialysis 5 times in a span of 8 days for azotemia with uremic symptoms at an outside facility, 3 weeks ago. He was positive for SARS CoV–2 and treated 1 month ago. Repeat nested RT PCR Throat/nasopharyngeal swab for SARS CoV–2 was negative with CT Chest not indicative of pneumonia. SARS CoV–2 Antibody using CLIA technique was positive. On evaluation, vitals stable, no anosmia, bilateral LMN facial weakness Left HB Gr IV>Right HB Gr III with difficulty in alternating jaw movements, poor lip seal, preserved sensation over the face and mouth. Preserved gag reflex, symmetrical velum elevation, normal motor power and reflex, with preserved sensory. Truncal ataxia noted on cerebellar examination.

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Mild restricted tongue range and speed of motion. Mild dysarthria with increased effort in speaking in connected speech with distortions for labial plosives, poor SMR. 3-tesla MRI brain with MRA was normal. Audiological evaluations (Table 1) indicated bilateral SNHL, poor speech discrimination scores, bilateral outer hair cell dysfunction, delayed absolute latencies and prolonged interpeak latencies of BERA with poor morphology in both ears was noted (Table 2) with bilateral vestibulo-collic reflex pathway dysfunction. Viral markers and vasculitis work up were negative for ANA, ANCA, ds–DNA. Normal upper and lower limb Nerve conduction study. CSF analysis showed albumin cytological dissociation. Anti-ganglioside antibodies were negative. He was treated with plasma exchange (5 cycles), haemodialysis (4 times) and IV corticosteroids. Clinical improvement was noted. On 3rd week follow up, he had considerable improvement in his Speech and Hearing abilities (Tables 1 and 2). Facial weakness was resolving Left HB Gr II, mild gait ataxia persisted but he was able to walk without support.

Case: 4

51-year-old lady presented with a history of 1-month duration of difficulty swallowing solids in the form of inability to chew, form bolus, sensation of food stuck in throat. Family reported nasal twang in voice while talking on phone noticed for about 2 weeks. Ptosis of left eye lid, coughing and choking on liquids gradually progressing 1-week duration. 1 month prior to developing symptoms, she had fever and cough, and did not seek appropriate medical attention due to inadequate facilities in the village. Nested real time RT PCR Throat/nasopharyngeal swab for SARS CoV–2 was negative with CT Chest not indicative of pneumonia. SARS CoV–2 Antibody using CLIA technique was positive. On examination, vitals stable, no anosmia, bi-facial weakness, left HB Gr III>right HB Gr II, reduced velar elevation, diminished gag–sensation preserved, normal jaw and tongue functions. Hyper nasal speech with nasal murmur. No perceivable voice or articulatory impairments. Proximal weakness grade 4+, normal sensory with normal cerebellar examination. Normal MRI Brain with MRA and contrast. Bedside swallow evaluation indicated slight anterior spillage on the left, increased effort in swallowing, delayed cough after swallow. Video-Laryngoscopy was normal. No gross or silent aspiration was noted during Video-Fluoroscopic Swallow Evaluation (VFSE). Mild to Moderate Oro-Pharyngeal dysphagia was evident with nasal regurgitation, delayed pharyngeal transit time and pharyngeal residue. Swallow rehabilitation was initiated focusing on pharyngeal strengthening, isometric and isotonic exercises. Nerve conduction study of upper and lower limb was normal. Absent ipsi R1 bilaterally, with preserved bilateral ipsi and contra R2 indicated bilateral involvement of trigeminal nerve/nuclei on Blink reflex test. Anti-ganglioside antibody profile was negative. CSF analysis showed albumin cytological dissociation. Intra Venous cortico-steroids were initiated. Clinical improvement in her facial weakness and swallowing abilities were noted.

RESULTS AND DISCUSSION

The Mechanism of action of Covid 19 can be described in the following manner.

TABLE 1
Audiological findings summary

Cases	Pure tone audiometry		Speech audiometry		Tympanometry	Reflexometry	OAE	c-VEMP
				During Admission				
Case 2	Right: 57 dB HL moderately severe SNHL	Left: 67 dB HL Moderately Severe to Severe SNHL	SDS: Right: 50% Left: 20%	SDS: Right: 50% Left: 20%	Bilateral 'A' type – normal compliance and peak pressure	Absent Ipsi–contra reflexes at maximum levels of stimulatiom	Bilateral absent DPOAE's at all frequencies	Bilateral absent P1–N1 complex at 95 dB nHL
				21 days after discharge				
	Right: 45 dB HL moderate SNHL	Left: 60 dB HL moderately severe to Severe SNHL	SDS: Right: 95% Left: 80%	SDS: Right: 95% Left: 80%	Bilateral 'A' type – normal compliance and peak pressure	Absent Ipsi–contra reflexes at maximum levels of stimulation	Bilateral Absent DPOAE's at all frequencies	Bilateral Absent P1–N1 complex at 95 dB nHL
				During Admission				
Case 3	Right: 52 dB HL moderate SNHL	Left: 48 dB HL moderate SNHL	SDS: Right: 40% Left: 30%	SDS: Right: 40% Left: 30%	Bilateral 'A' type–normal compliance and peak pressure	Absent Ipsi–contra stapedial reflexes at maximum levels of stimulation	Bilateral absent DPOAEs at all frequencies	Bilateral absent P1–N1 complex at 95 dB nHL
				21 Days after Discharge				
	Right: 25 dB HL, PTA1–41 dB HL moderate HF sloping SNHL	Left: 20 Db HL PTA 1–35 Db HL mild HF sloping SNHL	SDS: Right: 95% Left: 100%	SDS: Right: 95% Left: 100%	Bilateral 'A' type-normal compliance & Peak Pressure	Bilateral Ipsi–contra reflexes present at normal levels except at 4KHz	Bilateral DPOAEs present till Fdp–1003 Hz	Bilateral Absent P1–N1 complex at 95 dB nHL

TABLE 2
Auditory Brainstem Responses (BERA) findings during admission and 3 weeks after discharge

BERA 90 dB nHL for Click stimuli	Case 3				Case 2			
	Right Ear		Left Ear		Right Ear		Left Ear	
	III msec (mV)	V msec (mV)	III msec (mV)	V msec (mV)	III msec (mV)	V msec (mV)	III msec (mV)	V msec (mV)
				During admission				
Low rate 11.1/s	4.42 (0.11)	6.47 (0.23)	4.37 (0.07)	6.63 (0.18)	4.48 (0.12)	6.33 (0.39)	5.13 (0.22)	6.93 (0.35)
High rate 91.1/s	4.65 (0.07)	6.96 (0.19)	4.56 (0.03)	7.06 (0.13)	4.80 (0.09)	7.03 (0.28)	5.40 (0.08)	7.53 (0.24)
				21 Days after discharge				
Low Rate 11.1/s	3.93 (0.14)	5.97 (0.38)	4.14 (0.12)	6.10 (0.26)	3.75 (0.28)	5.85 (0.53)	4.15 (0.18)	5.90 (0.74)
High rate 91.1/s	4.12 (0.08)	6.19 (0.30)	4.23 (0.05)	6.27 (0.19)	4.23 (0.09)	6.23 (0.29)	4.40 (0.03)	6.15 (0.36)

Direct viral invasion

The potential target of SARS CoV-2 invasion is in the brainstem nuclei due to high expression of Angiotensin Converting Enzyme-2 (ACE 2), a possible mechanism of action in the cases described above [4]. The medullary trigeminal sensory nuclei and the vagus nuclei are the initial foci, leading to altered deglutition and persistent vomiting. The neurological manifestation of gustatory dysfunction arises from the disruption in medullary-thalamo-cortical connections. The nucleus of solitary tract being the first central relay for olfaction and deglutition integrates information from the Cranial Nerves V, VII, IX and X. Possibility of direct viral invasion into the nerve roots is ascertained by the absence of viral RNA in CSF1, although the time-course of evaluation and onset of symptoms may have an effect on this [5].

Brainstem inflammatory responses

The virus directly enters into Central Nervous System through the olfactory, trigeminal nerves, and travel *via* microglial cells and nerve sheath, as noted in non-human primates [6]. Direct viral invasion of the brainstem nuclei, medullary–thalamo– cortical networks may neurologically manifest as multiple cranial nerve palsies ranging from gustatory dysfunction to facial-bulbar weaknesses [7]. This invasion of the brainstem nuclei can evoke strong neuro inflammatory responses by microglial activation. Neuroinflammatory damage and injury to the brainstem nuclei can lead to demyelination or manifest as poly-cranial neuropathy with or without long tract signs, possible mechanism as noted in Cases 1, 2 and 3 described earlier.

Immune associated molecule induced damage

Absence of ocular paresis, preserved reflexes, absence of virus in CSF, absence of root enhancement in imaging, drastic response to immune modulators implicates auto immune mediated cranial nuclei involvement in Covid 19, as seen in Cases 3 and 4 discussed earlier [8]. The role of gangliosides in driving peripheral nerve auto immunity in Covid 19 is supported by evidence that describes involvement of glycoproteins along with spike protein in binding the virus to host ACE2 receptors. Possibility of cross reactivity between epitopes with spike bearing gangliosides and peripheral nerve glycolipids leading to molecular mimicry existing between other neurotrophic viruses that are known to trigger Guillain Barre Syndrome cannot be excluded. Hence, the anti-ganglioside antibodies may still be negative in such patients due to involvement of other mechanisms which are still not well understood [9]. Early initiation of Immuno-therapy should be considered when clinically indicated which will help in ameliorating cytokine effects, immune molecule associated damage and complete restoration of neurological status [10].

CONCLUSION

To understand the neuropathic, neuro invasive, neurotropic potential of Covid 19, specialists need to perform multidisciplinary, reliable measures of evaluation, screening for auto antibodies. All the 4 cases described have shown good neurological recovery over time with carefully chosen investigations and appropriate medical intervention and rehabilitation.

A potential high risk of progressive cell death, demyelination due to intense immune response, inflammatory molecular release is expected in this population. 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 can serve as a simple, non-invasive modality to evaluate and monitor acute and chronic sequelae of brainstem involvement, as noted in cases 2 and 3 with delayed peak latencies and poor speech discrimination scores indicating patterns of probable demyelination of auditory nerve. Combining other reliable non-invasive methods along with imaging can be useful measure of long-term effects of this novel virus on the central nervous system.

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