Neurological associations in auditory neuropathy spectrum disorder: Results from a tertiary hospital in South India

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Abstract

Aims: To find out the prevalence and types of neurological abnormalities associated in auditory neuropathy spectrum disorder in a large tertiary referral center. **Settings and Design:** A prospective clinical study was conducted on all patients diagnosed with auditory neuropathy spectrum disorder in the ear, nose, and throat (ENT) and neurology departments during a 17-month period. Patients with neurological abnormalities on history and examination were further assessed by a neurologist to determine the type of disorder present. **Results:** The frequency of auditory neuropathy spectrum disorder was 1.12%. Sixty percent were found to have neurological involvement. This included cerebral palsy in children, peripheral neuropathy (PN), spinocerebellar ataxia, hereditary motor-sensory neuropathy, spastic paresis, and ponto-bulbar palsy. Neurological lesions did not present simultaneously with hearing loss in most patients. Sixty-six percent of patients with auditory neuropathy spectrum disorder were born of consanguineous marriages. **Conclusions:** There is a high prevalence of neurological lesions in auditory neuropathy spectrum disorder which has to be kept in mind while evaluating such patients. Follow-up and counselling regarding the appearance of neuropathies is therefore important in such patients. A hereditary etiology is indicated in a majority of cases of auditory neuropathy spectrum disorder.

Key Words

Auditory neuropathy, Charcot-marie-tooth disease, consanguinity, Friedreich ataxia, genetic counseling, hereditary sensory, motor neuropathy, neurologic dysfunction, Refsum disease, sensorineural hearing loss

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Introduction

Auditory neuropathy (AN) is an uncommon disorder characterized by five integral features that distinguish it from other types of hearing loss. These are:

1. Sensorineural hearing loss of any degree,
2. With preserved otoacoustic emissions (OAEs) and /or cochlear microphonics (CM),
3. Auditory nerve dysfunction as evidenced by abnormal auditory brainstem evoked responses (ABR),
4. Poor speech perception with poor speech recognition score that seems out of proportion to the degree of hearing loss depicted by pure tone thresholds, and
5. Absent stapedial reflexes to the ipsilateral and contralateral tones at a 110-dB hearing level.[1]prematurity (n = 10 [45%]

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Peripheral neuropathy (PN) is not a constant finding in all patients with this hearing disorder. Some authors emphasize the dyssynchrony of temporal processing as the main pathology.[2] As new light is shed on AN, investigators find it is instead a syndrome (auditory neuropathy spectrum disorder or ANSD) and does not represent a single disease entity.[3] ANSD is an extremely varied disease in terms of age of onset and etiology which may range from neonate to adulthood; etiology from prematurity, kernicterus, birth hypoxia, ototoxic drug exposure, infection, and genetic. The mode of inheritance may be autosomal dominant, autosomal recessive, X-linked or mitochondrial.[4]

Studies have shown the association of neuropathies like Charcot-Marie-Tooth disease (CMT), Mohr-Tranebjaerg

syndrome, Refsum's disease, and Friedreich's ataxia with AN.[5-8]

Starr *et al*. have reported that ANSD was associated with a hereditary neurological disorder in 42% of their patients.[9] AN without the involvement of the neurological system has been termed as primary auditory neuropathy (PAN).[10] In this article we have highlighted the frequency and types of neurological involvement in ANSD.

Materials and Methods

The study was carried out in the ear, nose, and throat (ENT) and neurology departments of a tertiary referral center in southern India after approval by the institutional review board and followed guidelines set by the 1964 Declaration of Helsinki as revised in 2008. Adults and children presenting to the ENT outpatient during a 17-month period with hearing loss and complaints of difficulty in understanding speech and children referred for suspected hearing loss were included in this prospective study after obtaining informed written consent from all adults and guardians in case of minors. All patients underwent a detailed structured questionnaire and a full ear, nose, throat, and neurotological examination. Patients above 5 years then underwent pure tone audiometry, impedance audiometry, and speech audiometry. Those who had sensorineural hearing loss with absent acoustic reflexes and poor speech scores underwent an ABR and distortion product otoacoustic emissions (DPOAE). Children below 5 years underwent an ABR and DPOAE. Those with present DPOAE and absent or abnormal ABR were diagnosed as AN. If there was a suggestion of any neurological involvement a neurologist carried out a detailed examination and appropriate tests were ordered.

Procedure

Pure tone audiometry was done using GSI-61, Clinical two channel audiometer from Grason-Stadler, USA, MA-53 audiometers, MAICO Diagnostic GmbH, USA. Hearing thresholds up to 20 dB across the frequencies 250-4000 Hz were considered normal. Siemens SD-30 impedance audiometer was used to obtain immitance measurements. The test was performed using a probe tone frequency of 226 Hz. An ipsilateralstapedial reflex at 1000 Hz was elicited and considered normal if the level at which it was obtained fell between 70 dB and 100 dB. DPOAE testing was done with the smart DPOAE of Intelligent Hearing Systems, USA. DPOAE were recorded using a test protocol where preliminaries were fixed at L1 = 65 dB sound pressure level (SPL), L2 = 55 dB SPL with an f2/f1 ratio of 1.22. The f2 frequencies were carefully selected to correspond closely to audiometric test frequencies of 1000 Hz, 2000 Hz and 4000 Hz. A DPOAE response was considered to be present if the SNR >6.13 dB. The DPOAEs were recorded with DPOAE amplitude in dB SPL as a function of stimulus frequency. ABR was done using Intelligent Hearing systems launch pad version 1.0×. High intensity clicks were used presented at a rate of approximately 10 per second. Potential difference between an electrode on the vertex and ipsilateral stimulated mastoid were amplified in a band pass of approximately 30-30,000 Hz and averaged across a few thousand sweeps of 10-15 ms. Sampling rate was kept not lower than 20 kHz in order to avoid wave form distortions and to enhance latency resolution. The normal waveform included a series of 5-7 voltage oscillations approximately 1 millisecond apart during the first 6-10 ms after stimulus onset which confirmed the sequential transmission of synchronous action potentials of the eight nerve through the auditory pathway. The waves I to VII were labelled where V wave was the most positive in the complex. Patients with ANSD had an absent or abnormal ABR represented by waves I, III, and V when their level of hearing would typically result in measurable ABR responses. All patients with dizziness or imbalance also underwent a battery of tests with the computerized digital Electronystagmography Nystagmorite Mark II, Recorders and Medicare Systems (P) Ltd. 2007-2008.

Patients who were found to have neurologic involvement on history and examination by a neurologist were subjected to tests based on clinical findings; Nerve conduction studies (NCV), needle electromyography (EMG), multi-mode evoked potentials including visual evoked potentials (VEP) and somatosensory evoked potentials (SSEP), magnetic resonance imaging (MRI) of brain and spinal cord and sural nerve biopsies of sites affected were done. NCVs were done using Nicolet Viking Select, Natus Medical Incorporated, USA. The motor nerves tested were the median, ulnar, peroneal, and tibial nerves. The sensory nerves tested were the median, ulnar, sural, and superficial peroneal nerves. Needle electrode examination was done to look for spontaneous activity in the form of fibrillation, positive sharp wave discharges, and fasciculations. The motor unit potentials were assessed and the recruitment pattern noted. Multimode evoked potential studies included the VEP and SSEP. In VEP, the P100 latency was measured. SSEP was measured using surface electrodes at various points over the spine and scalp for recording the sequential wave forms reflecting the normal function/dysfunction of the afferent somatosensory pathway in median and tibial nerves. MRI was done appropriate to the clinical context.

Results

Of the total number of patients attending the ENT outpatient department at our tertiary referral center during 17 months (March 2007 to July 2008), an estimated 18,579 underwent hearing assessment. Among them there were 3120 with sensorineural hearing loss. Of these, 35 had AN. The frequency of AN over a 17-month period was 1.12% (35/3120). There were 22 males and 13 females, 5 were under-fives. The mean age of onset of ANSD was 13 years with a range of 3 months-26 years. The distribution of the 35 patients with ANSD is shown in [Figure 1]

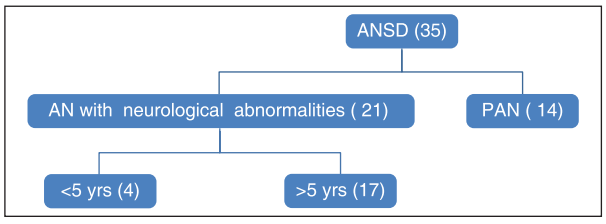

Figure 1: Flow chart showing distribution of patients with ANSD into different groups, ANSD = Auditory neuropathy spectrum disorder

Twenty one (60%) of the 35 patients with AN had abnormal neurological findings and were further assessed by the neurologist and additional tests done. The neurological profiles of the patients are given in Tables 1 and 2.

Four of the 5 children less than five-years of age (patients numbered 8, 14, 16, and 21) had associated neurological abnormalities. Of the four, one was diagnosed as evolving central motor delay with a generalized tonic clonic seizure disorder. Another child, 3 months of age had signs of pyramidal involvement. Two children were diagnosed to have cerebral palsy with pyramidal signs.

Of the 21 patients with neurological abnormalities, nine patients had evidence of PN; NCVs were done which showed pure sensory involvement in six, pure motor involvement in one and sensorimotor involvement in two. Among the 3 patients who underwent sural nerve biopsies, one had marked myelin loss while the other two had moderate loss of nerve fibres. Quadriceps muscle biopsy showed atrophic fibres in the patient with motor neuropathy.

Blood tests showed low Vitamin B12 levels in two of the 21 with neurological abnormalities and elevated blood lactate levels in all 4 of the family of BVVLS siblings and another two of the 21 patients. Six had a family history of similar neurological symptoms and four had history of neonatal insults like kernicterus, prematurity, low birth weight, and birth asphyxia.

Clinical study of a few representative cases

Patient number 6, an 18-year-old female with a family history (maternal uncle also having similar complaints) had features of bulbar palsy, anterior horn cell involvement, pyramidal tract involvement with signs of hypertonia, hypereflexia, and clonus, clinical features of cerebellar involvement, posterior column involvement both clinically, and confirmed by SSEP. Brain and spine imaging was normal. Optic nerve dysfunction was found on VEP [Figure 2] and a diagnosis of complicated hereditary spastic paresis was made.

Patient numbers 10, 11, 12, and 13 were siblings from the same family and their ages were 22, 20, 17, and 14 respectively at presentation. They had developed hearing loss around 13-years of age. Their electronystagmograms (ENG) were suggestive of bilateral peripheral vestibular pathology. Clinically all had temporalis muscle wasting with two having tongue fasciculation at rest. Their NCV showed mildly reduced sensory nerve action potentials (SNAP) in both sural nerves. Needle EMG showed spontaneous activity (fibrillation) from mentalis (Vll Nerve), temporalis (V Nerve), and tongue (Xll nerve). The study also showed evidence of bulbar muscle denervation, chronic denervation of C8/T1 myotomes, and a coexistent mild sensory neuropathy. Clinically these siblings had features consistent with Brown-Vialetto-Van Laere Syndrome (BVVLS).

Patient number 18 was a 16-year-old female with features of bulbar palsy, anterior horn cell involvement with tongue wasting and fasciculations, pyramidal tract involvement with signs of plasticity, hypereflexia and clonus, posterior column involvement with asymmetrical sensory neuropathy as shown on nerve conduction studies. On tibial SSEP, she had delayed cortical potentials indicative of dorsal cord dysfunction [Figure 3]. MRI showed features of

Table 1: Patient profile with regards to neurological evaluation in the 21 patients

Patient number	Age years	Sex	Limb		Abnormal gait	Sudden fall	Imbalance	Neuroaxis* involved	Neuropathy type	Neurologist diagnosis
			Weakness	Numbness						
1	18	F	yes	Yes	yes	no	yes	6	III	Peripheral sensorimotor neuropathy
2	19	F	no	No	no	no	no	2,6	II	NDD
3	28	F	no	No	yes	no	yes	5	NA	SCA
4	19	M	yes	Yes	yes	yes	yes	1,2,3,4,5	NA	BVVLS
5	23	M	no	No	no	no	no	4	NA	NDD
6	18	F	no	Yes	yes	yes	yes	1,2,3,4,5	NA	HSP
7	23	F	yes	Yes	yes	no	yes	5	NA	NDD
8	1.5	M	NA	No	NA	no	no	3,7	NA	CP
9	18	M	no	No	no	no	no	5	NA	NDD
10	14	M	yes	Yes	no	no	no	1,2,4,6	I	BVVLS
11	17	F	no	No	no	no	no	1,2,4,6	I	BVVLS
12	20	M	no	No	no	no	yes	1,2,4,6	I	BVVLS
13	22	M	no	No	no	no	no	1,2,4,6	I	BVVLS
14	0.25	M	NA	No	NA	no	NA	3	NA	NDD
15	21	M	no	No	no	no	yes	4	NA	NDD
16	2	M	NA	No	NA	no	NA	3,7	NA	CP
17	26	M	no	No	no	no	yes	4	NA	NDD
18	16	F	yes	Yes	no	yes	yes	1,2,3,4,6	I	SCA
19	14	M	no	No	no	no	no	4,6	I	NDD
20	15	M	yes	Yes	yes	no	yes	1,3,6	III	HMSN Type2
21	0.92	M	NA	No	NA	no	NA	3,7	NA	CP

SCA = Spinocerebellar ataxia, BVVLS = Brown-Vialetto-Van Laere syndrome, HSP = Hereditary spastic paresis, HMSN = Hereditary motor sensory neuropathy, NDD = No definite diagnosis made, NA = Not applicable, * see Table 2 for key, I = Sensory; II = Motor; III = Sensori-motor

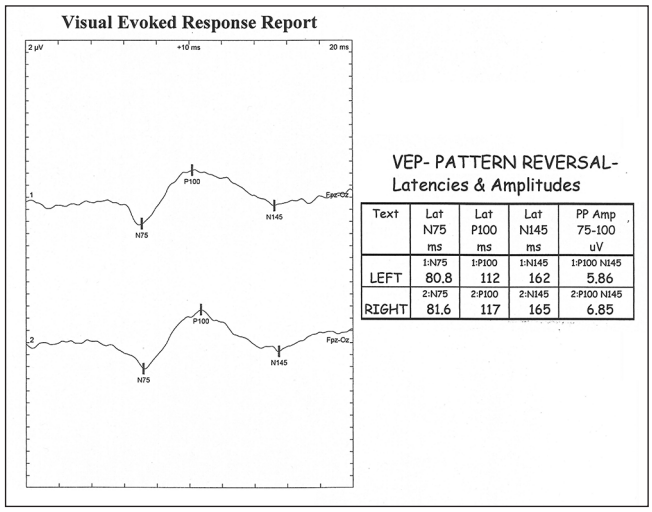

Figure 2: Visual evoked potential tracings showing bilateral anterior visual pathway dysfunction

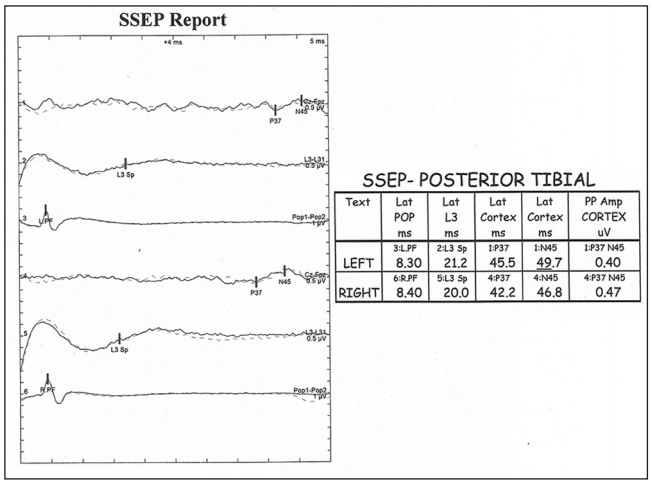

Figure 3: Posterior tibial somato-sensory evoked potential of a patient revealing bilateral central pathway dysfunction

Table 2: Types of neurological involvement

Subdivisions of neural axis	Numbers	Percentage
1,2,3,4,5	2	5.7
1,2,3,4,6	1	2.9
1,2,4,6	4	21.05
1,3,6	1	5.26
3	1	5.26
2,6	1	5.26
3,7	3	15.79
4	3	15.79
4,6	1	5.26
5	3	15.79
6	1	5.26
TOTAL (*n*)	21	100.00

1 = Bulbar palsy (bifacial, tongue wasting and fasciculations, nasal regurgitation and optic nerve dysfunction), 2 = Anterior horn cell involvement (wasting and fasciculation of limbs, hyporeflexia), 3 = Pyramidal involvement (hypertonia, hyperreflexia), 4 = Posterior column involvement (Romberg's, Dorsal column evoked potentials), 5 = Cerebellar (clinical/magnetic resonance imaging, MRI), 6 = Peripheral neuropathy (clinical/nerve conduction studies, NCV), 7 = Cerebral Palsy

cerebellar atrophy. She did not have a positive family history and was diagnosed to have a sporadic onset spinocerebellar ataxia.

Patient number 20, a 15-year-old boy with an uncle having similar symptoms and hearing loss had features of pyramidal tract involvement, bilateral distal muscle wasting, spasticity of lower limbs, bilateral optic nerve dysfunction and sensory motor PN on NCV was diagnosed to have hereditary motor-sensory neuropathy type 2 variant (CMT/ HMSN type 2).

Involvement of various subdivisions of the neural axis in the 21 patients is given in [Table 2].

Discussion

Our frequency of ANSD (1.12%) in the tertiary care setting is within what is reported by Cummings *et al*.[3] Vestibular lesions are known to be associated with ANSD but the extent of involvement and site of lesion is variable; though most often they tend to be of peripheral type.[11,12]

Named neurodegenerative conditions like Friedreich's ataxia, CMT, Madras motor neuron disease (MMND) and Refsum's disease are found to be associated with AN.[3,13]

The neuropathology in these conditions appears to be due to specific mutations causing abnormalities in different neuronal mitochondrial proteins.[7,8,13-15] More research points towards mitochondrial defects as fundamental pathology in these diseases.[16]

In our series, the presence of neurological abnormalities in AN was found to be 60% (21/35). ANSD can be associated with involvement of all regions of the neuroaxis like the cranial nerves, peripheral nerves, cerebellum, anterior horn cells and dorsal columns of the spinal cord. Patients with AN having PN seem to be a feature unique to the adult population.[9,17]

Nine subjects older than fifteen years demonstrated the presence of PN whereas no one younger than five years had any clinical evidence of PN. The timing of onset of PN associated with AN is unpredictable. In some, the hearing loss preceded the symptoms of peripheral weakness or sensory loss, while in others, the neuropathy came first. Starr et al. report that sural nerve biopsies from patients with clinical evidence of PN have rapidly progressive mixed axonal and demyelinating neuropathy.[5] Starr also reports 3 out of 10 who had apparent HMSN (CMT) and 5 had slight evidence of neuropathy clinically as well as on nerve conduction studies, two young patients (4 and 16 years old) had no sign of neuropathy.

Due to the insidious onset and slow progress of vestibular lesions, most patients are symptom free. Gait disturbances, falls and imbalance in these patients have been associated with neurological involvement. All 10 of our patients who complained of imbalance were found to have abnormalities of the neuroaxis suggesting that it could be an important clinical symptom indicative of neurological associations. Apart from

vestibular testing for these patients it is important to look for signs of other central involvement.

Congenital ANSD is mainly caused by genetic disorders and they may be expressed in isolation or manifest with a range of associated abnormalities. Non syndromic autosomal dominant inheritance of ANSD has been reported by Kim *et al*.[18] A few instances of non syndromic autosomal recessive type of ANSD have been described in literatures.[19,20] Genetic studies have shown mutations in OTOF gene which encodes otoferlin to cause AN associated with temperature dependant hearing loss.[21] Wang *et al*. identified a region on the X chromosome responsible for this disorder and called it the AN X-linked recessive locus 1.[22] There is a strong underlying genetic basis for ANSD associated with neurological abnormalities as seen in patients six and 20, and siblings belonging to one family; patients 10, 11, 12, and 13. These last four siblings were diagnosed to have BVVLS with an autosomal recessive type inheritance from disease-free parents of consanguineous marriage (uncle-niece).[23] Some cases of this entity are caused by mutations in the SLC52A3 gene which encodes the intestinal (hRFT2) riboflavin transporter.[24] Out of the 35 patients of ANSD diagnosed during this study 23 were born to parents of consanguineous marriage (10 of the 21 with neurological lesions). The custom of maternal uncle marrying his niece and marriage between first cousins is widely prevalent in this region of southern India in Hindu as well as in Muslim communities.[25] Further genetic tests are needed to study this in more detail among our patients. There is a strong association of neonatal hyperbilirubinemia in infants with acquired AN and conditions like low socioeconomic status and exposure to toxic chemicals have been postulated to play a role in late onset AN.[26,27]

Shivshanker *et al*. described 47 cases with no neuropathy clinically as well as on nerve conduction studies and they termed it as PAN.[10] In our study, out of five children with ANSD, four had an associated neurological disorder. Such a high association is likely because of the referral pattern to this tertiary center. India does not have a mandatory national universal neonatal hearing screening programme in place. Most children younger than five with hearing loss are presumably fitted with conventional hearing aids in smaller centers and the type of hearing loss remains undetected. When such children continue to have poor speech outcomes, they eventually get referred to tertiary centers and the referred subset is more likely to have ANSD.

Among the 30 adults with AN, we found 17 to have neurological abnormalities. These abnormalities were subclinical in most, with a positive history elicited only on probing and pointed questioning (eight patients). Further examinations revealed 21 patients with neurological findings. Although the common presentation of such patients is with hearing loss and difficulty in understanding speech, a detailed neurological history and examination results in identification of subtle neurological abnormalities and hence early referral to a neurologist. The hearing loss and neurological deficits also do not develop at the same time; one symptom may precede the other by several years. Gait abnormalities developed on an average of a year from the onset of hearing loss with a range of 0-5 years. Follow up of newly diagnosed cases of PAN is important in order to detect the neurological deficits as and when they manifest. Management of the hearing loss in these patients needs to be done in conjunction with the other abnormalities present and hence a multidisciplinary approach for rehabilitation is recommended. Counselling of patients and their families become important in the light of the strong associations with neural abnormalities.

There has been controversy surrounding the exact site of lesion in patients with AN. The area of involvement can be presynaptic (inner hair cells), synaptic or post synaptic.[28] The coexistence of other neuropathies in our patients suggests neuronal damage of peripheral or cranial nerves pointing to the site of lesion as postsynaptic.[29]

Management of these patients is supportive. Genetic testing and counselling should be offered. Physiotherapy to prevent limb contractures can minimize disability. There is no specific disease modifying therapy available yet that alters the course of disease. Riboflavin supplementation has been shown to improve outcomes and long term survival in some patients with BVVLS irrespective of whether plasma flavin and acylcarnitine levels were abnormal. In situations of resource crunch, a trial of riboflavin supplementation may be warranted in patients with ANSD and neurological involvement, pending further genetic tests.

Hearing rehabilitation should be started early for better communication outcomes. Conventional hearing aids as well as cochlear implantation have been found to be useful in patients with elevated hearing thresholds.[17] Recent studies have predicted good cochlear implant outcomes for children with ANSD.[30,31] One reason attributable to this is that even nerves that fire dyssynchronously in AN are better stimulated electrically with increased repeatability and precision than acoustically stimulated nerves.[32] There are relatively fewer reports of adult patients with ANSD undergoing cochlear implants as more commonly these patients have associated neuropathies and hence reservations about outcomes may be present. De Leenheer *et al*. reported three adults with ANSD, two of whom had associated neuropathies. These two patients with PN had improved outcomes compared to pre-implant scores.[33]

Conclusion

In our study we found neurological involvement in patients with AN to be quite high (60%). The range of abnormalities associated varied from cerebral palsy and seizure disorder in young children to PN, hereditary motor-sensory neuropathy, spinocerebellar ataxia, spastic paresis, and pontobulbar palsy in older people. A follow up of patients with AN should be done to detect any abnormalities which may appear later in life and patients should be advised regarding the appearance of such symptoms. Majority of the patients, who had abnormal neurological findings, had subclinical presentation and symptoms were elicited only with careful history taking and probing questions. A hereditary etiology is associated with a significant number of patients with ANSD. Genetic counselling and testing should be offered wherever feasible.

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Original Article

Neuropsychological markers of mild cognitive impairment: A clinic based study from urban India

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Abstract

Background: Mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia. Persons with MCI are at higher risk to develop dementia. Identifying MCI from normal aging has become a priority area of research. Neuropsychological assessment could help to identify these high risk individuals. **Objective:** To examine clinical utility and diagnostic accuracy of neuropsychological measures in identifying MCI. **Materials and Methods:** This is a cross-sectional study of 42 participants (22 patients with MCI and 20 normal controls [NC]) between the age of 60 and 80 years. All participants were screened for dementia and later a detailed neuropsychological assessment was carried out. **Results:** Persons with MCI performed significantly poorer than NC on word list (immediate and delayed recall), story recall test, stick construction delayed recall, fluency and Go/No-Go test. Measures of episodic memory especially word list delayed recall had the highest discriminating power compared with measures of semantic memory and executive functioning. **Conclusion:** Word list learning with delayed recall component is a possible candidate for detecting MCI from normal aging.

Key Words

Cognitive marker, cognitive test, memory assessment, mild cognitive impairment

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Introduction

Mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia and represents an early stage of Alzheimer's disease (AD).[1,2] Common characteristic of MCI is memory impairment beyond what is considered as normal for that particular age but with other relatively intact cognitive domains.[3,4] The diagnostic criteria for MCI includes memory complaint, abnormal memory function as compared to what is expected based on age and education, preserved general cognitive function, intact activities of daily living and absence of dementia.[5]

Mild cognitive impairment is linked with an increased risk for developing AD.[4,5] Currently there is no proven treatment for persons with dementia. Hence identification of this preclinical stage of dementia namely MCI has become a priority area in dementia research. Neuropsychological assessment has proven sensitive in discriminating between normal aging and mild cognitive impairment.[6,7]

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To the best of our knowledge, there is paucity of standardized indigenous neuropsychological measures for older Indian adults. However, attempts have been made to adapt screening instruments for Indian population such as Hindi Mental State Examination,[8] and Addenbrooke's Cognitive Examination.[9] Notwithstanding these tests are screening measures and involve rather easy items which may not be sensitive for differentiating between normal aging and MCI. Ganguli *et al*., (1996) adapted "Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Battery (CERAD-NB) for low educated Indian participants.[10] Ganguli and colleagues modified the original CERAD-NB, and eliminated and simplified several tests to suit illiterate participants. The Indian adaptation of CERAD-NB includes measures of memory and construction and could not assess several important cognitive functions like attention, working memory and executive functioning. However, despite its limitation it has been used to assess cognitive function of urban elderly people[11] and to estimate the prevalence of MCI.[12]

Recently, NIMHANS Neuropsychological Battery for the Elderly (NNB-E) has been developed and standardized for older Indian adults.[13] The clinical utility of the NNB-E for

Alzheimer dementia has been published in the recent times elsewhere.[14] The main objective of the present study was to examine usefulness of NNB-E in discriminating MCI. We were also interested in examining diagnostic accuracy/validity of different neuropsychological measures in identifying MCI.

Materials and Methods

The study sample consisted of 42 participants (22 patients with MCI and 20 normal controls [NC]) between the age range of 60 and 80 years. The two groups (MCI and NC) were matched for age and education. Patients with MCI were selected from the outpatient department of the Geriatric Services & Clinic, NIMHANS, Bangalore. All patients with MCI met the Petersen criteria[5] for MCI with clinical dementia rating (CDR) of 0.5.[15] Willing NC participants living independently in terms of their daily activities were recruited as controls. Participants were excluded if they had history of neurological/neurosurgical/psychiatric illness. A written informed consent was taken from the all participant before starting the assessment. The study was initiated after approval form ethics committee from the institute.

All participants initially were screened with Hindi Mental Status Examination and Every Day Abilities Scale for India. Later they were assessed in detail with the neuropsychological battery (NNB-E).

Hindi mental-status examination (HMSE)

Hindi mental-status examination[8] is a modified version of MMSE and is validated for Indian population. In this study, we used HMSE as a global cognitive screen.

Everyday abilities scale for India (EASI)

This is a 12-item brief measure of activities of daily living,[16] with norms, and is appropriate for use in evaluating dementia (along with other tests) in elderly people in India. This scale was used to detect difficulty in activities of daily living.

NNB-E

This is a brief, comprehensive and standardized neuropsychological battery,[13,14] developed for older Indian adults. The tests are described here briefly. Episodic memory was assessed with word list and story recall test assessing immediate and delayed recall. Attention was assessed by Span task and Picture cancellation task. Constructional ability was assessed with Stick construction test. Executive functions were assessed with Digit span, Corsi block-tapping test, fluency and Go/No-Go task and Tower of Hanoi. Language abilities were assessed by picture naming test and semantic verbal fluency test.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 12.0). Two-tailed Student's *t* test was used to examine statistical differences between MCI and NC on each neuropsychological test variables. The T test was used to examine homogeneity of the groups for age, education and the chi square was used for gender. Receiver operating characteristics (ROC) curve analysis was used to examine diagnostic accuracy of each test.

Results

The demographic characteristics of MCI and NC are presented in Table 1. There were no significant differences between the groups in terms of years of education, age and gender ratio. All participants with MCI were fully independent for their instrumental activities for daily life.

The neuropsychological performances of the two groups are presented in Table 2. Participants with MCI performed significantly lower than NC on memory and non-memory domains of cognition. The MCI group scored significantly lower on word list immediate recall (t = 3.20, *P* =.003), word list delayed recall (t = 7.11, *P* < .001), story recall test immediate recall (t = 3.70, *P* = 0.001), story recall test delayed recall (t = 5.05, *P* < .001), fluency for animals (t = 2.51, *P* = 0.016), Go/No-Go (t = 2.16, *P = 0*.043) and stick construction test delayed recall (t = 3.79, *P* = 0.001*)*.

Table 1: Demographic characteristics of the sample

	MCI	NC	*P* value
Age Mean years (SD)	68.18 (5.70)	68.65 (6.00)	.80
Education Mean years (SD)	13.60 (3.87)	13.75 (3.30)	.88
Gender (Male)	16	15	
HMSE Mean (SD)	28.00 (2.37)	30.00 (1.00)	.01
EASI Mean	0.00	0.00	.09

Table 2: Comparison of performance between MCI and NC group

Test variable (s)	MCI	NC	*P* value
Story Recall Test (IR)	8.65 (3.09)	11.70 (2.00)	.001
Story Recall Test (DR)	6.50 (3.75)	11.47 (2.49)	.000
Digit Span (F)	5.36 (1.00)	5.85 (1.34)	.48
Digit Span (R)	3.95 (1.04)	4.05 (1.14)	.09
Corsi block-tapping test (F)	5.14 (1.06)	5.50 (1.00)	.22
Corsi block-tapping test (R)	4.14 (1.15)	4.75 (1.11)	.09
Fluency (F)	9.77 (3.29)	11.75 (3.55)	.07
Fluency (A)	12.13 (4.60)	15.20 (3.23)	.016
Fluency (V)	9.90 (4.08)	13.15 (2.92)	.006
Word List (L_1)	4.04 (1.36)	5.00 (1.89)	.095
Word List (L_2)	5.54 (1.10)	7.05 (1.74)	.002
Word List (L_3)	6.18 (1.60)	7.84 (1.42)	.001
Word List (DR)	2.77 (1.63)	6.52 (1.74)	.000
Word List (Rec)	8.86 (1.90)	9.73 (1.00)	.06
Go/No-Go	1.19 (2.40)	.05 (0.22)	.043
Attention (Total Time)	234.00 (136.56)	167.00 (25.47)	.063
Tower of Hanoi (Move^1)	3.15 (0.48)	3.00 (0.00)	.190
Tower of Hanoi (Move^2)	14.40 (8.55)	11.70 (5.39)	.288
Tower of Hanoi (Move^3)	25.41 (10.80)	26.84 (10.22)	.737
Tower of Hanoi (Time^1)	10.05 (11.18)	5.73 (1.28)	.104
Tower of Hanoi (Time^2)	87.53 (58.53)	60.00 (35.53)	.106
Tower of Hanoi (Time^3)	165.33 (114.95)	118.23 (66.11)	.217
Stick Construction (IR)	20.31 (5.70)	22.78 (4.36)	.132
Stick Construction (DR)	8.22 (7.18)	15.91 (5.61)	.001

Constant score — Stick Construction copy, agnosia, apraxia, calculation

The area under the ROC curve (AUC) indicates how well any particular test discriminates between individuals with MCI and controls. A straight line (area = 0.5) indicates that a test is doing no better than chance in classifying dementia and control group, while a perfect scale would have a ROC curve with an area of 1. Receiver operating characteristics curve analyses revealed that Word list delayed recall had the highest AUC (96%) followed by Story memory delayed recall (84%). Word list delayed recall had better discriminatory power in terms of sensitivity and specificity [Figure 1 and Table 3].

Discussion

The main finding of the present study is that patients with MCI performed poorly on episodic memory, semantic memory and executive functioning. In the present study, we were able to demonstrate that NNB-E could discriminate between MCI and NC. Recent studies suggest that patients with MCI show deficits in multiple domains including memory,[17,18] semantic memory[19-21] and executive functioning.[17,22,23] This study also confirmed that patients with MCI have deficits in several domains including memory. Consistent with our observation, in the last decade, MCI is considered a heterogeneous group and therefore construct of MCI has expanded to include impairments in other cognitive domains.[4,5] MCI is divided into two subtypes: Amnestic MCI (single/multiple) and non-amnestic MCI (single/multiple). In our study, all participants met the criteria of amnestic MCI. It has been argued that participants with amnestic MCI are likely to develop AD and represents an early stage of AD.[1] The patients with MCI in this study need to be followed up to confirm it.

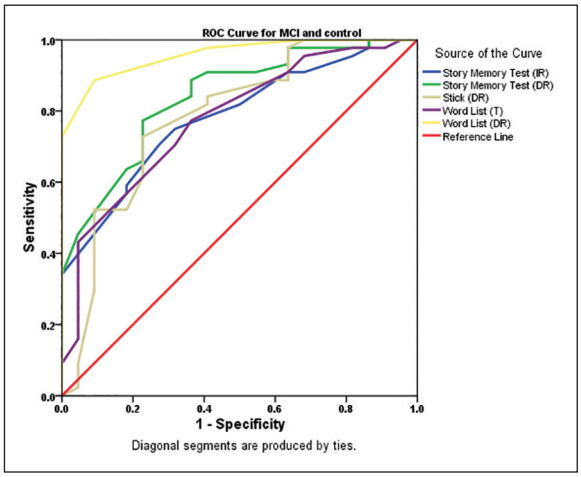

Figure 1: ROC curves of normal *vs* MCI

Our results indicate that the delayed recall on the Word list had the highest diagnostic accuracy in terms of sensitivity and specificity for discriminating between MCI cases and controls. Story recall test and Stick construction delayed recall had lesser discriminatory capacity (sensitivity and specificity). The results from the present study are consistent with other studies from West, indicating that measures of delayed recall were considerably more effective for detecting MCI than were measures of non-memory domains such as semantic fluency, executive functions or construction.[6,7, 24]

In our study, Word list was more sensitive than the other test of verbal learning and memory (Story recall test). These findings are consistent with the previous research, which indicates that Word list paradigm is more useful for examining verbal memory function compared with the story recall test.[10,25,26] It is well known that Word list involves several learning trials, which could result in better encoding and recall whereas story recall test involves a single learning trial that requires more active and effortful processing.[26] Therefore, better performance on story recall depends on several factors including executive functioning, processing speed and education.[25-27] Further research is needed to understand the role of executive functions and demographic variables clearly as well as their interactions in influencing performance on verbal learning measures.

Neuropsychological assessment is considered as gold standard tools for MCI. There are few culturally valid neuropsychological measures in India and none of the test has been validated for MCI. Based on our findings we suggest that NNB could be used as a sensitive tool for MCI.

There are several limitations of the present study. Our MCI sample was very small and future research is required on a larger sample to confirm the findings. We could have compared performance on NNB-E with other existing cognitive tests. However, there was lack of similar indigenous measure for older Indian participants. In our study, all participants met the criteria for amnestic MCI. Hence findings of the present study could not be generalized to non-amnestic MCI. Usefulness of NNB-E for other MCI groups should be examined in future research.

In conclusion, this is the first Indian study, which examined diagnostic accuracy of different neuropsychological measures using participants with MCI. We found that participants with MCI showed deficits in memory and executive functioning. However, measures of episodic memory and word list more specifically emerged as sensitive tool to identify MCI and could be potential cognitive marker for MCI.

Table 3: Area Under the Curve for NC and MCI

Test Result Variable(s)	AUC	Std. Error	*P* value	Cut-off	Sensitivity	Specificity
Word List (Delayed Recall)	.958	.021	.000	4	0.88	0.91
Story Recall Test (Delayed Recall)	.842	.049	.000	9	0.77	0.78
Story Recall Test (Immediate Recall)	.782	.056	.000	10	0.75	0.69
Word List Learning (Total)	.779	.059	.000	17	0.71	0.69
Sick Construction (Delayed Recall)	.770	.065	.000	11	0.71	0.78

AUC = Area under the curve

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