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Olivopontocerebellar Atrophy and Early Onset Cerebellar Ataxia with Retained Tendon Reflexes: A Neuropsychological Evaluation

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Abstract

To detect cognitive dysfunction in patients with progressive cerebellar degeneration, a prospective study on 25 patients (13 with olivopontocerebellar atrophy and 12 with early onset cerebellar ataxia with retained tendon reflexes) was carried out by using neuropsychological tests. The tests included NIMHANS Neuropsychological Battery for lobe functions in 17 patients and Binet Kamath test or Bhatia Performance Battery for assessment of intelligence in the rest. CT scan of head was done in 21 patients. Though historically none had cognitive dysfunctions, all the 17 patients had abnormality in at least one of the lobe function tests and the other eight patients had low 1Q. The most frequent abnormality was that of frontal lobe functions (88.2%), followed by that of temporal (81.2%) and parietal (68.7%) lobes. Impairment of visual learning and memory (83.3%), visual memory (75%), delayed response (66.7%) visuospatial-perception (62.5%), visual integration (53.3%) and kinetic melody (52.9%) were the principal findings. On IQ tests, patients showed impairment in conceptual thinking, visuo-motor coordination, non-meaningful memory and non-verbal reasoning. Though CT showed brain stem atrophy in all and cerebellar atrophy in 85.7%, only 38.1% patients had cortical and/or subcortical atrophy. It is suggested that cerebellum and/or its cortical connections may contribute to higher cognitive function in man.

Key words -
Cerebellar Ataxia,
Cognitive dysfunction,
Neuropsychological test,
Computed tomography

The role of cerebellum in modulating the higher order behaviour has been supported by recent clinical and research

reports [1], [2], [3]. The phylogenetically newest structures of the cerebellum may contribute to mental skills in much the same way that the phylogenetically older structures contribute to motor skills [4]. Apart from the motor functions, human cerebellum participates in many of the non-motor functions viz, counting, timing, sequencing, predicting and anticipatory planning, error-detecting and correcting, shifting of attention, pattern generation, adaptation, learning and language [3], [5]. Apart from the abnormalities of higher mental functions in cerebellar agenesis, cerebellar damage due to surgical resection, hereditary and acquired cerebellar diseases have also been reported to be associated with cognitive dysfunctions [1], [3]. Amongst the hereditary degenerative cerebellar disorders, various neuropsychological dysfunctions have been reported in patients of Friedreich's ataxia, [6], [7] olivopontocerebellar atrophies, [8], [9], [10], [11] ataxia telangiectasia [12], [13] and relatively selective cerebellar degeneration [14], [15], [16]. However, there are no detailed reports on patients with the recently described entity - "Early onset cerebellar ataxia with retained tendon reflexes" by Harding [17].

The present study, a part of a large prospective study on spinocerebellar degeneration, has attempted to delineate the neuropyschological deficits in patients with olivopontocerebellar atrophies (OPCA) and in those with early onset cerebellar atrophy with retained tendon reflexes (EOCA).

Materials and Methods

Patients

Twenty-five patients with progressive cerebellar degeneration seen in Department of Neurology at the National Institute of Mental Health & Neuro Sciences, Bangalore (NIMHANS), India over a period of two years (1990-1991) constituted the patient sample. Thirteen of them had OPCA and the rest belonged to EOCA group. Neuropsychological assessment, detailed clinical examination and electrophysiological tests were done in all and 21 patients underwent computed tomographic (CT) evaluation. The degree of disability of the patients was assessed by a functional disability score (FDS): 0 - no disability, 1 - mild disability (looks after oneself), 2 - moderate disability (needs help for self care), 3 - chair bound, and 4 - bed-ridden. Patients with only cerebellar signs (i.e, pure cerebellar ataxia), Friedreich's ataxia, ataxia telangiectasia and those with ataxia due to known causes (eg. alcohol, infarction, craniovertebral-junction anomalies, static encephalopathies) were excluded by appropriate investigations. The criteria of Harding [17] were used to select the 12 patients of EOCA. After excluding all the above types of ataxias, 13 patients were diagnosed to have OPCA on the basis of history, neurological examination and CT scan in majority (n= 10).

Neuropsychological evaluation

Of the 25 patients, in 17 patients detailed neuropsychological assessment was conducted to assess frontal, temporal, parietal and occipital lobe functions using the NIMHANS Neuropsychological Battery which contained tests standardised using operative and neuroradiological findings [18]. In the other eight patients the battery could not be used, either because of young age or poor cooperation. In six of them intelligence was assessed using the Binet Kamath test of intelligence [19] and the other two patients were evaluated on Bhatia Performance Battery of intelligence [20]. In addition, in two patients social functioning was assessed using Vine land Social Maturity Scale [21].

All the subjects were tested individually in several sessions.

NIMHANS Neuropsychological test Battery

Frontal lobe functions

Attention was assessed clinically, in terms of spontaneous arousal of attention, distractibility and

fatiguability of attention. A nominal scale was used to categorize it as adequate or inadequate. Allocation of voluntary attention was assessed using numerical and pictorial scanning. The numerical scanning test consisted of three parts. Part I consisted of numbers 1-20 and parts II and III of numbers 1-48 respectively. These numbers were randomly arranged and had to be crossed serially. Scores were derived from the time taken to complete parts I and II, the errors made in parts I and II and the numbers deleted in one minute in part three. Based on these scores, numerical scanning was termed adequate or inadequate.

Description of two pictures was the pictorial scanning test which was also scored as adequate or inadequate. Ideational fluency test had two parts. Patients recalled objects made of wood and round objects for two minutes each. Susceptibility to interference of memory was assessed by the delayed response learning test, wherein arithmetic problems were given. Performance was assessed on the time taken to complete and the accuracy. Adequacy of motivation, kinetic melody and expressive speech was clinically assessed on a nominal scale of adequate or inadequate functioning. Presence of personality change was also noted on a nominal scale.

Right temoral lobe

Visual integration was assessed using the object assembly subset of Wechsler Adult Performance Intelligence Scale (WAPIS) [22]. Four items were given; the mean time taken and the numbers correctly assembled were noted. Visual memory was assessed using the Benton Visual Retention Test: the number of cards correctly reproduced was the score [23]. Visual memory and learning was assessed by giving the complex figure test on three consecutive trials of 10 secs each, followed by recall. The fourth trial tested delayed recall after 10 minutes. This is a modification of the Ray Osterich figure [24]. The number of facts correctly reproduced was the score, the maximum being twenty.

Left temporal lobe

Receptive aphasia was tested by the verbal comprehension test, wherein 23 questions were asked orally and the number correctly answered were recorded. Sentence repetition test, wherein 20 sentences of increasing complexity were given assessed verbal memory. Number of sentences correctly repeated was noted. Logical memory was assessed by three successive presentation recall of a short passage. Delayed recall was evaluated after 10 minutes and the number of facts correctly reproduced was taken into account. On the basis of these tests the patients were described to have adequate or impaired left temporal lobe function.

Parietal lobe

Perceptual gestalt and spatial relations were the two tests used to assess visuospatial perception. Bender Gestalt test assessed perceptual gestalt whose adequacy was rated as present or absent. In the spatial relations test, a target pattern was compared to six other patterns, bigger in size. The patient had to detect one of the six which was identical to the standard. Accuracy and time were taken into account. Visuo-constructive ability was assessed using the block design test of WAPIS [22]. The first five patterns using four blocks each were given for construction. Number of patterns correctly constructed and the average time needed were taken into consideration. Adequacy of reading, writing and calculation were assessed. Focal signs of ideational and ideomotor apraxia, colour, visual object and tactile agnosias, body schema disturbances were scored on a nominal scale of present or absent.

Results

There were 19 men and 6 women. Age of the patients varied from 10 to 66 years (mean 31.4, SD 13.8 years) and duration of symptoms ranged from 3 months to 15 years (mean 7.0, SD 4.3 years). The educational levels of the patients were as follows: no formal education (n=6), below 10th standard (n=7), upto 12th standard (n=10) and graduation (n=2). Poor scholastic performance was seen in eight patients which was attributed to physical disability. Positive family history of similar illness was noted in 14 patients (autosomal recessive type: 10; autosomal dominant type: 4). Most frequent symptoms were swaying while walking, slurring of speech and shaking of hands. Details of the clinical findings are given in Table I.

Table I - Clinical features of patients with olivopontocerebellar atrophy and early onset cerebellar ataxia with retained tendon reflexes

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NIMHANS Neuropsychological battery

All the 17 patients had abnormality in at least one of the lobe function tests. The most frequent abnormality was in frontal lobe functions (88.2%) followed by that of temporal (81.2%) and parietal (68.7%) lobes. The details of results are given in Table II. One or more tests for assessment of temporal and parietal lobe functions could not be done in six and three patients respectively due to tremors of hand and/or poor cooperation.

Table II - Pattern of neuropsychological impairment in patients with olivopontocerebellar atrophy and early onset cerebellar ataxia with retained tendon reflexes

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The numbers in denominator indicate the patients on whom the tests could be performed.

Of the 17 patients who underwent lobe function tests, the EOCA patients had more frequent abnormalities in frontal (100% versus 81.8%) and temporal lobe function (100% versus 70%) tests as compared to OPCA patients. But reverse was the case with parietal lobe involvement viz. 80% and 50% in OPCA and EOCA respectively.

On a cross-sectional analysis, the severity of cognitive deficits of the patients in general had no correlation with the degree of disability or the duration of disease. A patient with symptoms of 3 months duration had frontal, parietal and temporal lobe dysfunctions, while another patient with 15 years of symptoms had only frontal and temporal lobe deficits. Moreover, it was often noticed that patients having FDS of two had more widespread cognitive deficits than a patient with FDS of three. On the contrary, while the degree of neuropsychological dysfunctions of the patients belonging to a given family was compared, there appeared to be a positive correlation with the duration of symptoms. This was brought out in patients of two such families. In one family (EOCA), while the elder sib had moderately severe frontal, parietal and temporal lobe deficits, the younger two affected sibs had only minimal frontal and temporal deficits. In the other family (OPCA), the elder sib had dysfunction of all the lobes while the younger affected sib had parietal and temporal lobe involvement. However, the

cognitive dysfunctions did not correlate with the physical disability.

IQ assessment

On Binet Kamath Test of intelligence and Bhatia Performance Battery of Intelligence, IQ levels of the eight patients ranged from 30 to 91 (average intelligence-1, dull normal-2, mild mental retardation-4, moderate mental retardation -1. The patients showed impairment in conceptual thinking, visuo-motor coordination, non-meaningful memory, nonverbal reasoning, meaningful memory, numerical reasoning, language and social intelligence. VSM showed gross delay in social age in the two patients studied.

CT study

Of the 21 CT scans, cerebellar hemispheric and/or vermian atrophy was present in 18 (85.7%). The various ratios of brain stem and cisterns when compared to normal controls showed significant atrophy of brain stem, especially of pons. Cerebral cortical and/or subcortical atrophy was present only in eight patients (38.1%) and leukoariosis in three patients (14.3%). Among them, two patients had cortical as well as sub-cortical atrophy. Thus 10 patients (47.6%) had atrophy of cerebellar hemisphere and/or leukoariosis. The pattern of cerebral cortical atrophy was diffuse (n=2), fronto-parietal (n=2), predominantly frontal (n=1) or parietal (n=1). Leukoariosis was either frontoparietal (n=2) or temproparietal (n=1) The incidence of cortical atrophy was equal in EOCA and OPCA patients.

Though all the patients had neuropsychological deficits there was no correlation between cortical atrophy and the deficits. There were patients with severe degree of cognitive impairment, who did not have cerebral cortical atrophy on CT scan. On the contrary, of the two patients with most severe (diffuse) cortical atrophy, one had minimal frontal lobe dysfunction and the other had mild mental retardation.

Discussion

All the patients of cerebellar ataxia in this study had some impairment on the neuropsychological evaluation but none had reported any symptoms related to higher mental function disturbances or dementia. Further, while a few (n=8) of them had poor scholastic performance it was essentially attributed to physical disability. The present study showed that the maximum impairment was noted in the frontal lobe and right temporal lobe functions. The abnormalities in frontal lobe functions were mainly in kinetic melody (though the tests were designed to give allowance for the motor disability), visual scanning, delayed response and ideational fluency.

Most patients had involvement of right temporal functions more than left. A large number of patients (62.5%) also had impairment of parietal lobe function and this fact along with impairment of visual learning and memory indicates that the main site of dysfunction is in the area of visuo-spatial perception.

Majority of the patients who underwent IQ assessment showed mild mental retardation and the deficits were in the conceptual thinking, visuo-motor coordination, non-meaningful memory and non-verbal reasoning suggesting frontal and temporal (especially right) lobe involvement, similar to the findings of formal neuropsychological tests. Cerebellar and/or brain stem atrophy was present in all the patients in whom CT scan was done (n=21). However, it is noteworthy that inspite of neuropsychological

impairment in all, only less than half of the patients (47.6%) showed atrophy of cerebral hemisphere and/or leukoariosis. The probable significance of this observation is discussed later.

Reports on detailed neuropsychological assessment in patients of EOCA are not available. Two of the 20 patients of EOCA described by Harding [17] were reported to have "subnormal intelligence". Ozeren et a1 [25] described 16 patients of EOCA of whom five were evaluated by Weschler Intelligence Scale for Children (Revised). Four had mental deficiency. On the contrary in the present study all the patients of EOCA had neuropsychological impairment.

Incidence of dementia in OPCA varies widely from 11.1% [26] to as high as 80% (Jellinger and Tarnowska-Dziduzko, 1971, quoted by Berent et a1 [10]). This may be due to differences in patient sample, criteria for diagnosis of OPCA, duration and stage of disease, methodologies of neuropsychological evaluation and follow-up of the patients. Data regarding detailed cognitive assessment in OPCA are sparse [9], [10], [11]. Kish et al [9] studied 14 patients with dominantly inherited OPCA from the Schut family. The patients scored on average within 20% of the controls in verbal and nonverbal intellectual abilities, naming attention and visuo-spatial functions. Quantitatively, more severe deficits were observed in memory testing and on tests of frontal system function. Information regarding the radiological evidence of cerebral cortical atrophy in the patients of these studies [9], [10], [11] are not available.Though the subjects of the study are not strictly comparable to those of the present study, the principal neuropsychological deficits in both the studies are almost similar.

El Awar et a1 [11] studied in detail the tests of delayed alternation (DA) and delayed response (DR) in 12 patients of the same group of dominantly inherited OPCAs as studied by Kish et al [9] and observed that performance of DA but not DR was impaired. In our study the delayed response task involved solution of arithmetic problems, wherein the initial part of the sum had to be remembered while hearing the subsequent part. Typical deficits involved forgetting the initial part. Thus it is similar to the delayed alternation task of El Awar et a1 [11] in that a sequence of information had to be retained in memory.

Berent et a1 [10] studied 39 patients of OPCA and found that abnormal intellect was present in only 10% of the patients and as a group the patients were not abnormal in general intellectual functioning and related cognitive abilities. The authors concluded that motor dysfunction, education and depressed mood might leave the patient with apparent cognitive dysfunction, when infact they were not. The results of our study contradicts these observations. The neuropsychological tests in our study had been designed to give allowance for motor disability and educational level. Moreover, Berent et a1 [10] cautioned about generalizing their findings to the larger universe of patients with OPCA, as the sample studied by them might have been a unique group. This is not surprising as the clinical features of OPCA has inter- as well as intra-familial variation, especially when studied cross-sectionally.

Contrary to the observation made by Kish et a1 [9] the present study did not find any positive correlation between the cognitive impairment and the severity of ataxia. Moreover, though the degree of impairment correlated with the duration of disease in a given family, it did not do so when the analysis was made cross-sectionally in the patients. The exact significance of this observation is not known. As stated before, it may be due to the different degree of phenotypic expression of the same disease in different families. Thus in a given family, the pattern of deficits and the expected correlation of increasing severity of a disease with duration may bold true. Again it is also possible that the education and level of literacy in different families may be responsible for earlier or delayed

appearence cognitive deficits, even though deficit may be as a result of the same genetic defect. This needs further evaluation.

There are no studies comparing the neuropsychological deficits in EOCA and OPCA patients. Our study included both EOCA and OPCA patients. Through there was a quantitative difference in abnortnalities between the two groups (EOCA patients had a higher incindence of frontal and temporal deficits), the pattern of cognitive dysfunction was similar in all these patients of hereditary ataxia. The present study is perhaps the first study to neuropsychologically evaluate EOCA patients in detail.

Short of autopsy and positron emission tomographic studies (for delineating metabolic activity), CT evidence of atrophic changes in human brain should give us atleast some information regarding the pathological substrates for neuropsychological abnormalities. Though all the CT scans showed either cerebellar or brain stem (includes cerebellar connections) atrophy, only 47.6% showed cortical, subcortical atrophy or leukoariosis This suggests two possibilities: either

(i) the neuropsychological tests are highly sensitive and detect mild cognitive impairment much before significant cortical or subcortical atrophy can be noted, or

(ii) the neuropsychological deficits are primarily due to involvement of cerebellum or its cortical connections.

The association areas in parietal, temporal and frontal lobes are responsible for integrative, complex, motivational activity and the fugal fibers from these areas after synapsing in the pons, pass through contralateral middle cerebellar peduncle and terminate in the cerebellar cortex. This corticopontocerebellar pathway is the principal means whereby information from the cerebral cortex converge to cerebellum. Studies in animals suggest that there is a locus in lateral pons that contains neurons responsive to multiple modalities and electrophysiologic recording from neurons in the dorsolateral pons have revealed direction specific visual responses [1]. The patients in our study had evidence of brain stem, especially pontine atrophy, thus explaining the predominant deficits in visuo-spatial perception and visual learning and memory. Moreover, the cerebellum probably regulates the speed, capacity, consistency and appropriateness of mental or cognitive process in the same way it regulates movements. Thus cerebellar lesion may produce a mismatch between reality and perceived reality and dysmetria of thought [1]. This may explain the features similar to frontal lobe dysfunction seen in patients with cerebellar degeneration, especially the impairment in ideational fluency, kinetic melody and delayed response. Memory deficit in ataxic patients may be related to the damage to the older cerebellar regions (floculonodular lobe, vermis and fastigial and globose nuclei) which is considered equivalent to limbic cerebellum.

The most recent data regarding the useful role of the cerebellum in human brain suggest that the ventrolateral part of dentate nucleus (neodentate) has evolved enormously in humans. The head is represented in it and it controls the cerebral prefrontal cortex (includes Broca's area and area 8) which contains symbolic representation of information, ideas or concepts [5]. The red nucleus and inferior olives of brain stem are the intermediate nuclei between the neodentate and prefrontal cortex [3]. Thus, it is not surprising that our patients with predominant cerebellar and brain stem atrophy had various cognitive dysfunctions.

It is true that in patients of OPCA and EOCA, there may be changes in cerebral cortex and basal ganglia later in the disease, which may produce cognitive dysfunction. However, there are recent studies [2], [14], [15] in patients of relatively selective cerebellar degeneration that showed similar deficits as observed in our study. Thus, all the neuropsychological deficits in our patients can be

explained by cerebellar degeneration and/or damage to the cortico-ponto-cerebellar fibers. This is also supported by the lack of significant cortical and sub-cortical atrophy in majority of the patients.

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