CLINICAL STUDY

Neuropsychological dysfunction in idiopathic hypoparathyroidism and its relationship with intracranial calcification and serum total calcium

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Abstract

Background: There is limited information on neuropsychological and neurological dysfunctions in patients with idiopathic hypoparathyroidism (IH).

Objective: To assess neuropsychological and neurological dysfunctions in IH and its associated factors in a cross-sectional design.

Method: Neuropsychological functions were assessed in 62 patients with IH and 70 controls using a battery of cognitive tests. Neurological assessment included extrapyramidal and cerebellar signs. Assessment of intracranial calcification and volume of basal ganglia calcification (BGC) were made on computed tomography and of calcium control by averaging serum total calcium values available during the follow-up.

Results: A significantly higher proportion of patients with IH showed neuropsychological dysfunctions than controls (32.3 (95% CI: 20.9–45.3) vs 5.7% (95% CI: 1.6–14.0), $P < 0.001$). Neurological signs were present in 35.5% patients (extrapyramidal: 16.1%; cerebellar: 20.9%). Volume of BGC and number of sites with intracranial calcifications including cerebellum/dentate were comparable in patients with and without neuropsychological, extrapyramidal or cerebellar dysfunctions. Cognitive dysfunction score was lower by 1.7 points in males than in females ($P = 0.02$) and increased by 0.21 and 5.5 for each year increase in the duration of illness ($P = 0.001$) and one unit increase in serum calcium–phosphorus product ($P = 0.01$) respectively. The scores improved by 0.27 for every mg% increase in serum calcium ($P = 0.001$).

Conclusion: Neuropsychological dysfunctions are present in up to one-third of patients with IH and correlate with duration of illness, female gender, serum calcium and calcium–phosphorus product during follow-up but not with intracranial calcification. These dysfunctions may affect their daily functions, safety and drug compliance.

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Introduction

Hypoparathyroidism is characterised by hypocalcaemia, hyperphosphataemia and inappropriately low serum PTH levels (1). These patients often receive intermittent calcium therapy for tetany and convulsions before definite diagnosis. At presentation, intracranial calcification is present in 74% of them, which usually begins in the basal ganglia region involving lenticular, caudate nuclei and spread to thalamus, cerebellum and other areas of brain (2). Presence and progression of calcification correlates with the duration of symptoms and calcium:phosphorus ratio maintained by the patients (2).

The clinical significance of basal ganglia calcification (BGC) in hypoparathyroidism is not clear but has been linked to neuropsychological and neurological

dysfunctions such as impaired attention, memory, information processing, executive function and extrapyramidal symptoms (3, 4, 5, 6). Idiopathic hypoparathyroidism (IH) is a rare disease and there is paucity of data on the frequency of neuropsychological dysfunctions and their associated factors among them. This study was carried out to assess the prevalence of neuropsychological and neurological dysfunctions and their relationship with BGC and serum total calcium maintained by the patients.

Materials and methods

Patients with IH attending the endocrine clinic of the All India Institute of Medical Sciences during 2010–2012

were enrolled. The diagnosis of IH was based on the clinical features, hypocalcaemia, hyperphosphataemia, normal serum creatinine, low serum PTH levels and absence of post-surgical or syndromic hypoparathyroidism as described earlier (7, 8, 9). Criteria for inclusion were i) availability of computed tomography (CT) scan films of head not before 2 years of assessment of neuropsychological dysfunctions and ii) sufficiently literate to perform all the cognitive functions tests. Patients with history of head injury, intracranial illness and mental retardation were excluded. Age at onset of hypocalcaemic symptoms and presentation to the hospital, duration of hypocalcaemic symptoms, socio-economic and educational status, neuropsychological assessment, and intracranial calcification were recorded in predesigned proforma. Details of serum total calcium and inorganic phosphorus values at presentation and their average values during follow-up in the clinic and in the month of cognitive assessment were also noted. None of the patients had history of alcoholism or cerebrovascular accidents.

Patients were on regular follow-up and received 1–2 g elemental calcium and 0.5–2.0 µg 1- α -(OH)D/day orally and were monitored three monthly for serum total calcium, inorganic phosphorus and urinary calcium excretion. The therapy was adjusted to maintain their serum total calcium in the range of 8.0–8.5 mg/dl and calcium excretion of ~100–150 mg/day. Neuropsychological evaluation, determination of sites of calcification and assessment of volume of BGC and average serum total calcium maintained were described as follows:

Neuropsychological assessment

Cognitive and psychiatric dysfunctions were assessed by a trained psychologist (S K) using a battery of nine standard tests administered in a fixed order (10). All the subjects were assessed separately in a session lasting 2–3 h between 1100 and 1400 h. Various tests used included: i) Hindi Mental State Examination (HMSE) to assess orientation, arithmetic, memory and language (11); ii) Brief Psychiatric Rating Scale (BPRS) for psychopathology (12); iii) Trail Making Test (TMT-A/B) assessing visual attention, psychomotor speed and task switching (13); iv) Abnormal Involuntary Movement Scale (AIMS) to measure abnormal movements (14); v) The PGI-Memory scale (PGIMS) for memory (15); vi) Bender Gestalt Test (BGT) for visuo-spatial gestalt functioning and micrographia (16); vii) Finger Tapping test (FTT) for psychomotor deficits (17); viii) Verbal Adult Intelligence Scale (VAIS) to assess verbal quotient (VQ) (15); ix) Benton Visual Retention Test (BVRT) for visual perception, visual memory and visual constructive abilities (18); and x) Stroop test for executive function and response inhibition (19). Quality of physical and mental health was assessed by Short Form (SF-36) questionnaire (20). These tests have been used earlier in the Indian population for the diagnosis

and assessment of severity of cognitive dysfunction (21, 22, 23, 24, 25). Corrections for age and education were applied to the raw scores of PGIMS and VAIS tests. HMSE used in the current study is an adaptive version of MMSE validated for the Indian population (11, 26). The cognitive tests were standardised for inter- and intra-personal variations. Details of the tests used and the criteria adopted to define impaired functioning are given in Table 1. All these tests were also carried out in apparently healthy subjects with similar age (within ± 2 years) and sex in order to have normative values for comparative purpose. These controls were unaffected attendants of admitted patients of various endocrine illnesses and had normal serum total calcium and phosphorus values. Controls who were not sufficiently literate to perform all the cognitive functions tests were excluded.

Definitions of impaired cognitive functions

The raw scores of each cognitive function test were compared between patients and the controls. The frequency of impaired cognitive dysfunction was analysed using standard cutoffs for HMSE, AIMS and VAIS (11, 14, 15). BPRS, TMT, BGT and BVRT tests were categorised as impaired when the raw scores of the respective tests were more than upper quartile of the values observed in the healthy controls. PGIMS, Finger Tapping and Stroop tests were categorised as impaired when the raw scores of these tests were less than the lower quartile of these observed in the healthy controls. These percentiles were selected in order to have adequate numbers in each category so that results obtained were stable.

A global cognitive dysfunction score was calculated by combining abnormalities observed in HMSE, TMT-A, TMT-B, AIMS, BGT, FTT, VAIS, BVRT, PGIMS and Stroop (Colour, Word and Colour–Word) tests. Each of these tests was scored as '1' when impaired and '0' if normal. The sum of these scores represented the global cognitive dysfunction score. Prevalence of neuropsychological dysfunction in IH was assessed based on the frequency of subjects with global cognitive dysfunction score >90th percentile of the controls, indicating the presence of six or more abnormal cognitive tests. This study was approved by the Institutional Ethics Committee and written informed consent was obtained from the patients and controls.

Neurological assessment

Neurological examination included tests for muscle strength, wasting, gait disturbances, involuntary movements, hypotonia and cortical sensation by two-point discrimination test and graphesthesia. Cerebellar functions were assessed by finger–nose test, tandem walking, heel–shin test and dysidiadochokinesia. Abnormalities in the basal ganglia function were assessed by extrapyramidal signs including limb rigidity,

Table 1 Summary of the various neuropsychological tests, their interpretation and criteria for impairment (P=percentile).

Test	Description	Scoring	Criteria for impairment
Hindi Mental State Examination (HMSE)	30-Point questionnaire measuring orientation arithmetic, memory and language	Each correct point answer is scored 1	Normal ≥ 24 , impaired < 24
Brief Psychiatric Rating Scale (BPRS)	18-Item rating scale assessing psychopathology	Maximum score = 126 score proportional to psychopathology	Impaired > 22 (P ₇₅)
Trail Making Tests A and B	Part A: 25 numerically numbered circles randomly drawn on a paper assessing visual attention	Part A: time taken to connect the circles	Part A = Impaired ≥ 45 s (P ₇₅)
	Part B: circles with numerical (1–13) and letters (A–L) assessing visual attention, task switching	Part B: time taken to draw lines to connect the circles in an ascending pattern alternating with letters	Part B = Impaired ≥ 102 s (P ₇₅)
Abnormal Involuntary Movement Scale (AIMS)	12-Item rating involuntary movements of the body	None = 0, minimal = 1, mild = 2, moderate = 3, severe = 4	Score ≥ 2 indicates abnormal movements
PGI-Memory scale (PGIMS)	Score standardised on Indian subjects aged 20–45 years to assess verbal and non-verbal memory	Each correct answer gets a score of 1. Higher score indicates better functioning	Impaired < 72 (P ₂₅)
Bender Gestalt Test	Nine figures measuring visuo-spatial gestalt and micrographia	Total number of errors based on Hain's method (taken from PGI-BBD)	Impaired ≥ 3 (P ₇₅)
Finger Tapping	Six patterns of rhythmic tap with fingers of both hands on the table for psychomotor deficits	Score of 1 for each correct pattern	Impaired < 4 (P ₂₅)
Verbal Adult Intelligence Scale (VAIS)	Based on information, comprehension, arithmetic and digit span measuring verbal intelligence	Based on age, education norms validated on Indian population	Impaired VQ < 80
Benton Visual Retention Test (BVRT)	Ten geometrical figures measuring visual perception, memory and constructive abilities	Total number of errors based on type of errors	Impaired ≥ 8 (P ₇₅)
The Stroop Colour and Word Test	Colours written in black ink on page 1 (C); letters written in colour on page 2 (W) and words are written in different colours on page 3 (CW). Subject is asked to name the colour with which word is written. Test measures executive functions, response inhibition and cognitive flexibility	Number of correct responses in 45 s	Impaired less than C: impaired < 34 (P ₂₅) W: impaired < 50 (P ₂₅) CW: impaired < 19 (P ₂₅)

VQ, verbal quotient.

resting tremor, arm swing and mask-like faces. Micrographia was assessed by BGT, which showed a reduction in the size of figure drawn during assessment.

Computed tomography

All the CT scan films were assessed by an expert radiologist (R S) and two other authors (R G and S A). The presence of calcification at basal ganglia (globus pallidus, putamen and caudate), thalamus, cerebellum, dentate nucleus and periventricular region including central semiovale regions was recorded. Figure 1 shows representative scans of sites of intracranial calcification observed in patients with IH. Each site affected was scored as 1. Besides, presence of calcification in the frontal, parietal, occipital and temporal lobes was also recorded.

Volume of lenticular nuclei (putamen and globus pallidus) calcification was recorded as described earlier (2). Briefly, the length and width of the calcification at the lentiform nucleus were measured in the axial CT scan showing maximum area of calcification using the scale in the film. The height was obtained by adding slice thickness of the CT sections showing lentiform calcification, and the volume was recorded in cm³.

Assessment of average serum total calcium

Average serum total calcium for each patient was assessed by taking the mean of the values available i) at presentation, ii) during each follow-up and iii) on the day of assessment of cognitive function assessment.

Figure 1 Non-contrast axial CT images of the brain in three patients with IH showing (A) normal scan, (B) calcification in the basal ganglia region involving caudate nucleus, globus pallidum and putamen and (C) calcification in the cerebellum and basal ganglia.

Biochemical assessment

Serum total calcium, inorganic phosphorus and alkaline phosphatase were measured (Hitachi 917; Roche; normal range (NR): 8.1–8.5, 2.5–4.5 mg/dl and 80–240 IU/l respectively) as described earlier (2), with intra and interassay coefficients of variation 3.5–5.0%. Serum 25(OH)D was measured using chemiluminescence (DiaSorin, Inc., Stillwater, MN, USA) with levels <20 ng/ml considered deficient, 20–30 ng/ml insufficient and 30.0 ng/ml or more as sufficient. Serum iPTH was measured using IRMA till 2006 (DiaSorin, minimum detection, 0.7 ng/l; NR, 13–54 ng/l) and afterward by chemiluminescence assay (Elecsys-2010; Roche; NR, 15–65 ng/l).

Statistical analysis

Quantitative data are reported as mean and s.d. and qualitative data as frequencies in percentages. Student's *t*-test and Wilcoxon rank sum test were used to analyse the differences in various quantitative characteristics between patients and controls, among patients with and without intracranial calcification and between patients with and without cognitive impairment. The normality of the data was assessed using Shapiro–Wilk test. Qualitative variables were compared using χ^2 test. Spearman's rank correlation coefficients of cognitive dysfunction score with volume of intracranial calcification and with number of sites of intracranial calcifications were calculated. Multiple regression was used to determine variables associated with the presence of neuropsychological dysfunction among IH cases. *P* values were adjusted using Bonferroni correction method for multiple comparisons. All *P* values were two-tailed, and values <0.05 were considered significant. All statistical analyses were implemented on Stata 11.1 (StataCorp., College Station, TX, USA).

Results

A total of 76 patients came for follow-up during the study period. All of them agreed to participate. However,

14 of the 76 patients were excluded (CT scan not available=1, mental retardation=2, history of head injury=1, acoustic neuroma=1 and illiterate=9). Final analysis was carried out in 62 patients and their clinical characteristics shown in Table 2 were similar to the usual pattern reported earlier (2). The mean serum 25(OH)D values in male and female patients were significantly different (37.5 ± 16.80 vs 28.7 ± 13.46 ng/ml, $P=0.02$).

Seventy-four controls were contacted and all agreed to participate in the study. However, four who were not sufficiently literate to perform the entire cognitive test were excluded. The 70 healthy controls enrolled were of similar age (37.4 ± 15.22 years) and M:F ratio (37:33). The level of education was comparable between cases and controls (primary level educated 8.6 vs 9.7%; primary to 12th standard 42.9 vs 40.3%; graduate level 17.1 vs 19.3% and postgraduate level 31.4 vs 30.6% respectively, $P=0.98$).

Prevalence of cognitive, psychiatric and neurological dysfunctions

The mean global cognitive dysfunction score was significantly higher in patients with IH than in the controls and 32.3% (95% CI: 20.9–45.3) of the patients had a global cognitive dysfunction score more than the 90th percentile of controls. Table 3 shows the average raw scores and the frequency of impairment in various cognitive and psychiatric tests in patients and the control groups. Patients with IH had significantly higher impairment in all the cognitive tests than the controls. Correction for multiple testing made the difference in HMSE and AIMS between cases and controls insignificant.

The mean raw score and the proportion of subjects with neuropsychiatric disturbances on BPRS were significantly higher in patients than in controls (25.5 ± 5.66 vs 20.3 ± 2.72 and 66.1 vs 24.3% respectively, $P<0.001$, Table 3). Patients with IH showed a significantly higher proportion of abnormalities (mild or more) than the controls in the items

Table 2 Clinical characteristics (means and s.d.) of the 62 patients with IH.

Parameters	Data
Male:female (n)	35:27
Age at onset of hypocalcaemic symptoms (years)	24.5 ± 14.10
Age at current study (years)	36.6 ± 15.16
Duration of hypocalcaemic symptoms (years)	12.0 ± 8.77
History of seizures (%)	69.4
Intracranial calcification (%)	88.7
Cataract (%)	44.1
Serum total calcium (mg/dl)	5.4 ± 0.94
Serum inorganic phosphorus (mg/dl)	7.0 ± 1.52
Intact PTH (pg/ml)	8.2 ± 8.85 (median 5.0)

Table 3 Comparison of raw scores (means $\pm$ s.d.) and frequency of impaired neurocognitive tests in the patient and control groups.

Test	Hypoparathyroid (n=62)	Controls (n=70)	P	P*
Global Cognitive Dysfunction Score				
Raw score	4.6 $\pm$ 3.36	2.2 $\pm$ 2.58	0.000005	<0.001
% Impaired (≥ 6)	32.3%	5.7%	0.00008	0.001
Verbal Adult Intelligence Scale (VQ)				
Raw score	88.4 $\pm$ 11.94	92.4 $\pm$ 8.23	0.0275	0.36
% Impaired (VQ <80)	29.0%	8.6%	0.002	0.03
Hindi Mental State Examination				
Raw score	26.4 $\pm$ 3.26	27.2 $\pm$ 2.09	0.31	0.99
% Impaired (score <24)	17.7%	5.7%	0.03	0.39
Brief Psychiatric Rating Scale				
Raw score	25.5 $\pm$ 5.66	20.3 $\pm$ 2.72	<10 ⁻⁸	<0.001
% Impaired (score >22)	66.1%	24.3%	0.0000013	<0.001
Trail Making Test (A)				
Raw score (s)	61.9 $\pm$ 47.43	40.6 $\pm$ 22.89	0.00053	<0.01
% Impaired (time taken ≥ 45 s)	56.4%	25.7%	0.0003	<0.01
Trail Making Test (B)				
Raw score (s)	126.0 $\pm$ 74.01	88.2 $\pm$ 50.47	0.0004	<0.01
% Impaired (with time taken ≥ 102 s)	45.2%	25.7%	0.019	0.25
Abnormal Involuntary Movement Scale				
% Impaired (score ≥ 2)	9.7%	0.0%	0.008	0.10
Benton Visual Retention Test				
Raw score	9.9 $\pm$ 5.03	5.4 $\pm$ 2.97	<10 ⁻⁷	<0.001
% Impaired (no. of errors ≥ 8)	62.9%	25.7%	0.000017	<0.01
Stroop Word				
Raw score (no. of correct words read)	53.9 $\pm$ 21.87	67.0 $\pm$ 22.67	0.00097	0.01
% Impaired (score <50)	48.4%	24.3%	0.0039	0.05
Stroop Colour				
Raw score (no. of correct colours read)	45.0 $\pm$ 16.81	50.8 $\pm$ 17.55	0.08	0.99
% Impaired (score <34)	22.6%	17.1%	0.43	0.99
Stroop Colour–Word Combination				
Raw score (no. of correct word–colours read)	27.7 $\pm$ 13.44	35.4 $\pm$ 16.09	0.0036	0.05
% Impaired (score <19)	22.6%	10.0%	0.0486	0.63
Bender Gestalt Test				
Raw score (total no. of weighted errors)	4.4 $\pm$ 3.93	2.2 $\pm$ 2.47	0.0007	<0.01
% Impaired (score ≥ 3)	61.3%	32.9%	0.0011	0.01
Finger Tapping Test				
Raw score (no. of correct patterns)	3.7 $\pm$ 1.81	4.6 $\pm$ 1.33	0.004	0.05
% Impaired (score <4)	38.7%	21.4%	0.03	0.39
PGI-Memory scale Total	71.0 $\pm$ 11.37	76.6 $\pm$ 8.53	0.0013	0.02
% Impaired (score <72)	46.8%	25.7%	0.012	0.16
SF-36-PCS	44.8 $\pm$ 9.49	52.6 $\pm$ 7.90	0.000001	<0.001
SF-36-MCS	43.3 $\pm$ 10.26	45.8 $\pm$ 8.75	0.25	0.99

*P values corrected for multiple testing. VQ, verbal quotient.

assessing somatic concern (25.8 vs 0.0%, $P < 0.001$), anxiety (46.8 vs 17.1%, $P < 0.001$), presence of guilt feelings (17.7 vs 2.9%, $P < 0.01$), tension (54.8 vs 20.0%, $P < 0.001$), mannerism and posturing (9.7 vs 0.0%, $P < 0.01$), depressive mood (40.3 vs 12.9%, $P = 0.001$), hostility (30.6 vs 4.3%, $P < 0.001$) and suspiciousness (8.1 vs 0.0%, $P = 0.02$). No significant difference between patients and controls in other domains in BPRS could be observed.

The physical health-related quality of life score on SF-36 was significantly lower in IH patients than in the controls. Twenty-two (35.5%) patients had impaired neurological examination involving cerebellar signs in 19.4%, extrapyramidal signs in 14.5% and both in 1.6% of them. Cerebellar signs included impaired tandem walk ($n = 13$) and abnormal heel–shin/finger–nose coordination ($n = 3$). Extrapyramidal signs included

mask-like face and/or rigidity ($n = 4$), reduced arm swing ($n = 2$) and micrographia ($n = 7$). Clinically overt Parkinson's disease requiring levodopa therapy was present in two patients.

Relationship between cognitive and neurological dysfunctions with intracranial calcification

There was no significant correlation between global cognitive dysfunction score and volume of calcification ($r = -0.008$, $P = 0.95$) or intracranial calcification site score ($r = -0.02$, $P = 0.85$). The mean global cognitive dysfunction score was comparable for patients with ($n = 55$) and without ($n = 7$) any intracranial calcification (4.6 $\pm$ 3.35 and 4.7 $\pm$ 3.64 respectively, $P = 0.93$). The average volume of lenticular calcification was

similar in hypoparathyroid patients with and without impaired cognitive function tests (Table 4) and in patients with and without signs of cerebellar and extrapyramidal dysfunction (6.3 ± 9.68 vs 9.0 ± 11.14 cm³, $P=0.60$ and 3.9 ± 3.88 vs 9.3 ± 11.53 cm³, $P=0.31$ respectively).

Similarly, the frequency of cerebellar signs was comparable in patients with ($n=38$) and without ($n=24$) cerebellar calcification (impaired tandem walk, 23.7 vs 16.7%, $P=0.51$ and impaired finger–nose and/or heel–shin test, 5.3 vs 4.2%, $P=0.84$).

Relationship between cognitive and neurological dysfunction with average serum total calcium

The average number of serum total calcium and phosphorus values measured for each patient during follow-up was 13.0 ± 8.04 (median = 12.5) and their

mean values were 7.3 ± 1.18 and 5.9 ± 1.33 mg% respectively. The mean serum total calcium at the time of assessment of neuropsychological dysfunction among patients was 7.7 ± 1.20 mg% (range: 4.8–10.5 mg%). The average serum total calcium from presentation to the follow-up was significantly lower in patients with impaired Stroop Word test, which turned to insignificant after correction for multiple testing (Table 4).

The average serum total calcium values for patients with and without extrapyramidal and cerebellar signs were comparable (6.8 ± 0.66 vs 6.8 ± 0.74 mg% ($P=0.83$) and 6.7 ± 0.77 vs 6.8 ± 0.72 mg% ($P=0.62$) respectively).

Factors associated with cognitive dysfunction

To assess the factors associated with cognitive dysfunctions in IH, multiple regression analysis was carried out with cognitive dysfunction score as the dependent

Table 4 Volume of BGC and serum total calcium levels (mean $\pm$ s.d.) in hypoparathyroid patients with and without impaired neuropsychological tests.

Cognitive tests	n	Volume of BGC (cm ³)	P	Calcium (mg%)	P
Global cognitive score					
Normal	42	8.6 ± 10.19		6.8 ± 0.76	
Impaired (score ≥ 6)	20	8.0 ± 12.36	0.44	6.6 ± 0.65	0.30
Verbal Adult Intelligence Scale (VQ)					
Normal	44	8.2 ± 10.75		6.9 ± 0.72	
Impaired (VQ < 80)	18	9.0 ± 11.32	0.63	6.5 ± 0.70	0.07
Hindi Mental State Examination					
Normal	51	8.4 ± 10.86		6.8 ± 0.69	
Impaired (score < 24)	11	8.5 ± 11.23	0.60	6.5 ± 0.85	0.26
Trail Making Test (A)					
Normal	27	9.6 ± 10.87		6.7 ± 0.76	
Impaired (time taken ≥ 45 s)	35	7.6 ± 10.88	0.43	6.8 ± 0.70	0.45
Trail Making Test (B)					
Normal	34	10.0 ± 11.78		6.8 ± 0.78	
Impaired (time taken ≥ 102 s)	28	6.5 ± 9.42	0.34	6.7 ± 0.66	0.63
Abnormal Involuntary Movement Scale					
Normal	56	8.9 ± 11.22		6.8 ± 0.72	
Impaired (score ≥ 2)	6	4.3 ± 4.81	0.26	6.7 ± 0.87	0.74
Benton Visual Retention Test					
Normal	23	7.7 ± 9.23		6.9 ± 0.77	
Impaired (no. of errors ≥ 8)	39	8.9 ± 11.77	0.65	6.7 ± 0.69	0.18
Stroop Word					
Normal	32	8.7 ± 11.07		7.0 ± 0.73	
Impaired (score < 50)	30	8.2 ± 10.77	0.67	6.6 ± 0.66	0.03
Stroop Colour					
Normal	48	8.2 ± 9.97		6.8 ± 0.74	
Impaired (score < 34)	14	9.1 ± 13.82	0.99	6.6 ± 0.70	0.23
Stroop Colour–Word Combination					
Normal	48	9.1 ± 11.14		6.9 ± 0.71	
Impaired (score < 19)	14	6.1 ± 9.70	0.52	6.4 ± 0.68	0.02
Bender Gestalt Test					
Normal	24	8.9 ± 11.21		6.8 ± 0.82	
Impaired (score ≥ 3)	38	8.2 ± 10.73	0.72	6.7 ± 0.67	0.47
Finger Tapping Test					
Normal	38	7.3 ± 9.86		6.9 ± 0.73	
Impaired (score < 4)	24	10.2 ± 12.23	0.43	6.6 ± 0.67	0.06
PGI-Memory scale Total					
Normal	33	8.5 ± 11.25		6.8 ± 0.74	
Impaired (score < 72)	29	8.4 ± 10.54	0.90	6.7 ± 0.71	0.33

VQ, verbal quotient.

variable and age, gender, average calcium and inorganic phosphorus maintained during follow-up, calcium:phosphorus ratio and presence of intracranial calcification as independent variables. On average, males had a lower impaired global cognitive dysfunction score by 1.7 ($P=0.02$) compared with females, implying female patients with IH had impaired test results in two more cognitive tests than males. Cognitive impairment score increased by 0.21 ($P=0.001$) for each year of increase in the duration of hypocalcaemic symptoms and decreased by 0.27 ($P<0.001$) for every 1 mg% increase in average serum calcium during follow-up. For every 1 unit increase in calcium phosphorus product, the cognitive score increased by 5.5 ($P=0.01$). Serum 25(OH)D and PTH showed no significant correlation with global cognitive dysfunction score ($r=0.10$, $P=0.46$, and $r=0.08$, $P=0.53$ respectively).

Discussion

Neuropsychological dysfunctions in hypoparathyroidism have been a topic of interest for the past several decades. However, the disease is rare and most of the information on cognitive dysfunction in IH is based on isolated case reports or series of patients (3, 4, 5, 6, 27, 28). Denko & Kaelbling (29) reported intellectual impairment in 19% of patients and unclassifiable psychiatric symptoms in 14%. Kowdley *et al.* (5) performed a formal assessment of cognitive dysfunction in a case-control study and reported 65% prevalence of dementia and neuropsychological dysfunctions such as impaired attention, task switching and ability to initiate concept development in response to verbal instructions in patients with hypoparathyroidism. This study consolidates the existing knowledge with the strengths of i) a large cohort, ii) an homogeneous group of patients without confounding factors of mental retardation often associated with pseudohypoparathyroidism, iii) age and gender comparable controls, iv) assessment of neuropsychological functions by a team including a psychiatrist, psychologist, neurologist, radiologist and endocrinologist and correlation of neuropsychological dysfunction with intracranial calcification and calcaemic control.

This study revealed neuropsychological dysfunction in one-third (32.3%) of patients with IH. Besides confirming the neuropsychological dysfunction reported earlier in hypoparathyroidism, the current study reveals presence of additional dysfunctions such as intellectual impairment, psychomotor deficits, response inhibition, impairment in visuo-spatial gestalt functioning, visual perception constructive abilities and micrographia. The additional dysfunctions detected could be because we employed a broad base of cognitive tests unlike the previous reports that assessed mainly prefrontal cortex, basal ganglia and thalamus (5). The neuropsychiatric abnormalities such as anxiety and

depression on BPRS observed in 66% of IH are similar to those reported by Yang *et al.* (6). Management of such patients of IH with increased psychiatric disturbances and its comparability with similar patients without IH is subject for further studies.

Besides the neuropsychological dysfunctions, this study revealed neurological signs in one-third (34.9%) of patients with IH. Extrapyramidal signs were present in 16% of patients with two of them having Parkinson's disease requiring levodopa therapy. Yang *et al.* (6) observed extrapyramidal symptoms in 8.5% of IH. There is no previous study systematically assessing the prevalence of cerebellar dysfunctions in IH. Interestingly, in this study, we observed cerebellar signs in 21% of the patients.

The mechanism for neuropsychological, extrapyramidal and cerebellar dysfunction in hypoparathyroidism is not yet clear. These dysfunctions could be due to the disruption of the corticostriatal tract carrying sensory input from cerebral cortex to striatum (caudate and putamen) for relay to globus pallidus, which fine tunes the sensory input along with dentatothalamic tract and projects the signals back to the cortex for organised activity (30). Presence of intracranial calcification at multiple sites along with chronic hypocalcaemia might result in disruption and/or dysfunction of this flow leading to affective, extrapyramidal and cerebellar dysfunction. By this logic, one would expect a greater impairment in these dysfunctions in patients with intracranial calcification. Kowdley *et al.* (5) observed a weak correlation between neuropsychological dysfunction and volume of calcification. However, we observed no significant association of neuropsychological, extrapyramidal and cerebellar dysfunction in IH with presence of calcification, number of sites of intracranial calcification and volume of BGC.

There is no systematic study assessing relationship of cognitive dysfunction in IH with serum calcium status maintained by the patients. In the current study, the average duration of hypocalcaemic symptoms at assessment of neuropsychological dysfunction was 12 years. These patients were on our follow-up and received oral calcium and 1- α -(OH)D for the control of hypocalcaemic symptoms and maintaining a target serum total calcium of 8.0–8.5 mg/dl. The broad range of serum total calcium (7.3 ± 1.18 mg%) attained during follow-up allowed analysis of its relationship with neuropsychological dysfunction in IH. Regression analysis showed serum total calcium and its product with phosphorus as independent predictors of neuropsychological dysfunction in IH. These facts suggest the importance of long-term serum calcium and phosphorus control in possible prevention of psychological dysfunction in IH.

While this study has revealed new information, there are limitations. The number of patients with IH and intracranial calcifications was small. The lack of relationship between neurocognitive and neurological

dysfunction with intracranial calcification could be explained by several possible mechanisms that were not assessed in this study. Patients in this study were young with a mean age in the third decade. Presence of neuropsychological dysfunction might show an association with intracranial calcification with advancing age. A prospective follow-up of patients with intracranial calcification and IH and their comparison with age-matched controls would help in this regard. Besides, we have not studied the density of the calcification or the impact of intracranial calcification on the blood flow or dopaminergic transmission in the basal ganglia or cerebellar region. Calcium–phosphorus–hydroxyapatite deposition in the perivascular, neuronal synapse regions and cellular parenchyma may affect cognitive function differently. Calcification occurring predominantly in the perivascular region or synaptic regions of the corticospinal tracts could result in impaired blood flow/hypoxia and impaired dopamine and glutamate transmission respectively. Further studies assessing glucose metabolism of basal ganglia and cerebellar regions with [^{18}F]-FDG-PET and dopaminergic neurotransmission by [^{18}F]-Fluoro-Dopa PET and $^{99\text{m}}\text{Tc}$ -TRODAT SPECT scans and their correlation with intracranial calcification and neurocognitive and neurological dysfunctions would be helpful to elucidate on this issue (31, 32).

Type 2 PTH receptors are present in cerebral and cerebellar cortex and other areas crucial for cognition such as amygdala, hypothalamus and thalamus (33). Though this study showed no significant association between serum PTH level and cognitive score, future studies incorporating long-term PTH therapy for IH might be more helpful to understand the relationship between cognitive dysfunction and PTH.

The reasons for higher neurocognitive dysfunction in female patients with IH than in males are not clear. Though in this study female patients had lower mean 25(OH)D than males, they had near normal values of 25(OH)D. Further, the global cognitive score did not correlate with vitamin D status. There is a possibility that poor cognitive performance of females with IH is reflective of the generally marginalised performance of females in the developing countries like India, which were attributed to socioeconomic and cultural reasons (34).

High prevalence of neuropsychological dysfunction such as impaired visual attention, concentration, memory loss, rhythmicity and dementia may affect patients' safety and their daily activities such as driving, maintenance of personal hygiene, nutrition and drug compliance. In view of the above, counselling of patients and their family members can be part of management especially in females and in those with longer duration of IH.

To conclude, patients with IH demonstrate neuropsychological dysfunction in up to one-third and cerebellar and/or extrapyramidal signs in one-fifth of cases respectively. These dysfunctions correlate with duration of hypocalcaemic symptoms, serum total calcium and

calcium–phosphorus maintained in follow-up, but not with the presence or extent of intracranial calcification. In view of the high prevalence of neuropsychological dysfunctions in patients with IH, periodic neuropsychological assessment may be warranted so that appropriate counselling can improve their day-to-day functioning including drug compliance.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

R Goswami has designed and supervised the study and has clinically treated the patients included in this study and also managed their clinical and biochemical data for the past 12 years. S Aggarwal, S Kailash, R Sagar and M Tripathi carried out neuropsychological and neurological assessment in the study. R Sharma read the CT scans. V Sreenivas analysed the data. N Gupta carried out the biochemical assays. All the authors contributed to the writing of the manuscript.

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