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REVIEW

The association between hypoparathyroidism and cognitive impairment: a systematic review

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Abstract

Context and purpose Hypocalcemia and low parathyroid hormone levels have been commonly suggested as factors able to induce central nervous system disturbances. However, evidences on the occurrence of cognitive impairment are limited or underestimated. The aim of this review is, therefore, to systematically summarize the available evidence concerning the occurrence of cognitive impairment among subjects suffering from idiopathic or secondary hypoparathyroidism.

Methods A systematic selection of the available literature was performed by searching the online databases PubMed, Scopus and Web of Knowledge.

Results The present systematic review included sixteen case report articles and one cross-sectional controlled study. Case reports were the most representative literature sources and involved ten women and seven men. The presence of cognitive impairment was mostly discussed in association with idiopathic hypoparathyroidism (HPT); five articles described the occurrence of cognitive impairment following postsurgical HPT. The case-controlled study reported a significant presence of peculiar cognitive deficits (e.g. reduced inhibitory control, impairment in visuo-spatial functioning among, and psychomotor retardation) among HPT subjects compared to healthy controls, with serum total calcium and its product with phosphorus as independent predictors of neuropsychological dysfunctions.

Conclusion Even though mostly based on single case reports, the presence of neuropsychological dysfunctions in the context of HPT appears to be a consistent core finding.

Keywords Hypoparathyroidism · Parathyroid · Hypocalcaemia · Cognitive functions · Cognitive impairment

Abbreviations

SCD	Subjective cognitive decline
MCI	Mild cognitive impairment
PTH	Parathyroid hormone
BBB	Blood brain barrier
HPT	Hypoparathyroidism
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
WAIS	Wechsler Adult Intelligence Scale
PTH2R	PTH 2 receptor
GPCRs	G protein-coupled receptors
TIP39	Tuber infundibular peptide of 39 residues

Introduction

The term cognitive functioning refers to a wide range of multiple mental abilities, which commonly include learning, memory, reasoning, problem-solving, decision-making, and attention processes [1]. Cognitive functioning follows different and heterogeneous trajectories along the entire lifespan, which substantially explain the individual differences in the processes of adaptation to cognitive aging [2]. A commonly shared assumption is that the variance in cognitive functioning proportionally increases with age; consistently, the presence of a general age-related progressive cognitive decline has been supported by several clinical evidences, which acknowledge processing speed, delayed recall, working memory and attention as the most impaired domains [3, 4].

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The evaluation and the monitoring of cognitive functioning over time represent an established routine in clinical practice, since the progression of cognitive impairment is considered a relevant key factor leading to dementia. In this context, nosographic constructs, such as subjective cognitive decline (SCD) and mild cognitive impairment (MCI), and their evolution, have been broadly investigated as features of neurodegenerative disorders, or in association to several comorbid conditions, such as heart failure [5], diabetes [6], kidney failure [7], or bone-related chronic medical conditions [8].

Due to the lack of a resolutive pharmacological approach to the progression of cognitive decline towards dementia, the investigation of potential modifiable risk factors related to cognitive impairment has gained interest increasingly over the past years. In this perspective, dysfunctions of parathyroid hormone (PTH) have been discussed in several studies in relation to the onset and the maintenance of cognitive impairment, since PTH is able to cross the blood brain barrier (BBB), and several PTH receptors are additionally present in the human brain [9–11].

In the context of parathyroid dysfunctions, hypoparathyroidism (HPT) is commonly considered a rare endocrine condition, as suggested by the relatively low prevalence rates estimated among different clinical populations. Consistently, a large consultation of clinical databases in the United States (US) has rated a prevalence of 25 cases/100,000 subjects per year, consisting in estimated 77,000 cases in a population of nearly 300 million individuals [12]. A recent investigation throughout hospital registries in Italy has estimated a prevalence of approximatively 5 cases/100,000 individuals per year, even though this selection of cases might be too restrictive [13].

The main endocrinological features of HPT are the presence of hypocalcemia and absent or low serum PTH levels; the shared treatment is based on calcium and vitamin D supplementation [14]. This condition can present as idiopathic or secondary, such as the postsurgical form, which is not uncommon after thyroid and parathyroid surgery [15].

The clinical picture of HPT may be comprehensively characterized by a wide range of signs and symptoms including seizure, muscle cramps, paraesthesia, tetany, cardiac alterations, as well as mental and cognitive disturbances [16–18]. Additionally, an established neuroradiological marker of HPT has been broadly acknowledged in the presence of symmetric subcortical calcifications, which are frequently localized in the basal ganglia, as well as in other sites, such as thalamus and dentate nuclei [17].

Hypocalcemia and low PTH levels have been suggested as factors able to induce central nervous system disturbances [18, 19]; however, evidences on the occurrence of cognitive impairment are limited or underestimated.

To further address this topic, the aim of this review is to systematically summarize the available evidence concerning the occurrence of cognitive impairment among subjects suffering from idiopathic or secondary hypoparathyroidism.

Methods

Search strategy

A systematic review of the available literature was conducted in two steps. First, the studies were retrieved from the online database PubMed, Scopus and WebOf Knowledge, by matching the following keywords: “hypoparathyroidism”, "hypoparathyroid disorders", “dementia”, “cognitive”, “cognitive functions”, and “cognitive impairment”. A preliminary filter on the online search was applied by language (English) and species (Humans). Additionally, the reference lists of the included studies were examined to identify further potentially relevant studies missed during the database search. The online search was definitively completed on May 15, 2020.

Inclusion and exclusion criteria

Original, English-written research articles with an available full text, investigating the association between HPT and cognitive impairment were included in the current systematic review. Articles had to provide information on diagnostic criteria and/or clinical signs of HPT (e.g. laboratory test, neuroimaging evidence). Additionally, a clear description of the impaired cognitive domains was necessary, as well as information on the used cognitive assessment tools had to be showed. Since we expected to potentially retrieve articles published several decades ago, we also included those with at least a sufficiently reliable description of cognitive symptoms that was provided.

Retrieved articles that did not provide sufficient information on the patients’ medical condition and/or the cognitive assessment were excluded.

Eligibility screening

The eligibility of each article was assessed through a three-step procedure, by two different authors (AS, FB): the first-step screening was carried out by accounting the title, the second-step screening by accounting the abstract, and the final-step screening by accounting the full text. Conflicts regarding eligibility were resolved by consulting a senior author (AC). The review articles were not screened for eligibility; however, they were considered as a further source for potential studies not previously identified.

Data extraction

Data were extracted according to the following preliminary coding protocol shared by all the authors. From each study, general information was first extracted (i.e. author, year of publication, study design); we also collected information on the type of investigated patients, and their relative medical history. Additionally, data regarding the HPT diagnosis (laboratory and neuroradiological evidence), as well as regarding the cognitive assessment (i.e. symptoms, evaluation tools) were collected. If present, we also extracted pre–post pharmacological treatment data regarding patients' cognitive and/or clinical status.

Quality assessment

The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (https://joannabriggs.org/critical_appraisal_tools) was used to evaluate the quality of the majority of included studies, which were case reports. The checklist ascertains the presence of several methodological aspects (e.g. the description of case's demographic and anamnestic information, the validity of employed diagnostic tools, the description of procedures and results), through a four-response scoring (i.e. yes, no, unclear, not applicable).

Additionally, to evaluate the quality of the sole retrieved case-controlled study, we used the Newcastle–Ottawa Scale (NOS) (www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for case-controlled studies, as previously suggested [20]. The scale rates the quality of studies by the evaluation of three aspects (i.e. selection, comparability, and outcome), and it allocates a maximum of nine stars for the highest quality.

Two independent authors (AS, FB) assessed the methodological quality of the retrieved articles to identify any potential source of bias. Disagreements were resolved by consensus with a senior author (AC). A summary of the quality assessment of included studies is provided in Table 1; explicatory models of the two quality assessment tools are provided as Supplementary Materials.

Results

Literature search results

A summary of the screening procedure is provided in the PRISMA flow diagram (Fig. 1). The initial web search strategy retrieved 103 papers; the additional independent manual search retrieved further eight articles. After removing duplicates, eighty-eight articles were screened according to title/abstract criterion. Twenty-eight full-text articles were consequently assessed for eligibility. Finally, seventeen studies were included in the current systematic review.

Included studies

The present systematic review included sixteen case report articles [21–36] and one cross-sectional controlled study [37]. The main characteristics of the included studies are summarized in Table 2.

Case reports

Case reports were the most representative literature sources and involved ten women and seven men; patients' age ranged from 57 to 77 years (mean age 68.2 ± 6.76 years) among women, and from 25 to 80 years (mean age 51.42 ± 18.85 years) among men. The presence of cognitive impairment was mostly discussed in association with idiopathic HPT (eleven case reports); five articles [25, 28–30, 36], involving six patients, described the occurrence of cognitive impairment following postsurgical HPT; the surgery was undergone generally due to goiter, and in one case due to thyroid adenoma.

Each study provided both laboratory and neuroradiological evidence supporting the diagnosis of HPT. Accordingly, brain calcifications were commonly detected through CT scans, involving subcortical regions, such as the basal ganglia. The majority of reports shared the presence of hypocalcemia, hyperphosphatemia and low PTH as laboratory evidence of HPT. In one case [27], the diagnosis of HPT was eventually confirmed even though normal calcium levels, and reduced PTH, 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D levels were found in a 51-year-old man suffering from progressively worsened cognitive disturbances. A further peculiar report was described by Heckmann and colleagues that documented the case of a 74-year-old woman, who had previously undergone thyroidectomy, presenting hypercalcemia and decreased PTH levels, and complaining a progressive cognitive decline. Since the diagnosis of secondary HPT was disclosed, the unusual presence of hypercalcemia was eventually referred to a drug overdosage for previous hypocalcemia episodes [29].

In the majority of the discussed case reports of idiopathic HPT, patients referred to clinical observation suffering from cognitive disturbances, whose onset ranged from few weeks [21, 32], few years [23, 26, 31, 33], to approximately a decade before the visit [24]. Conversely, in one case, a female patient came to observation for the progression of cognitive disorders over the last year, with a diagnosis of idiopathic HPT already disclosed more than a decade before [34]. In the reported case by Terada and colleagues, the temporal relationship between the onset of cognitive symptoms and

Table 1 Quality assessment of the included studies

JBI checklist for case reports								
Study	Complete demographic characteristics	Patient's history	Current clinical condition	Assessment/ diagnosis	Treatment procedure	Post intervention condition	Adverse events	Takeaway lessons
Robinson et al. (1954)	No	Yes	Yes	No	Yes	Yes	No	No
Eraut (1974)	No	Yes	Yes	Yes	Yes	Unclear	No	Yes
Mateo and Gimenez-Roldan (1982)	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Lorusso et al. (1994)	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Nicolai and Lazzarino (1994)	No	Yes	Yes	Yes	Yes	Unclear	No	No
Roca et al. (1995)	No	Yes	Yes	Yes	Yes	Unclear	No	Yes
Stuerem-burg et al. (1996)	No	Unclear	Yes	Yes	Yes	Yes	No	Yes
Galvez-Jimenez et al. (2000)	No	Yes	Yes	Yes	Yes	Unclear	No	Yes
Heckmann et al. (2000)	No	Unclear	Yes	Yes	No	Yes	No	No
Adorni et al. (2005)	No	Unclear	Yes	Unclear	No	No	No	No
Titlic et al. (2008)	No	Unclear	Yes	Yes	Unclear	Unclear	No	Yes
Katsidzira et al. (2010)	No	Yes	Yes	Yes	No	No	No	Yes
Kumar et al. (2013)	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Moreno et al. (2015)	No	Yes	Yes	Yes	Yes	Unclear	No	Yes

Table 1 (continued)

JBI checklist for case reports

Study	Complete demographic characteristics	Patient's history	Current clinical condition	Assessment/ diagnosis	Treatment procedure	Post intervention condition	Adverse events	Takeaway lessons
Terada et al. (2015)	No	Yes	Yes	Yes	No	No	No	Yes
Dos Santos et al. (2016)	No	Yes	Yes	Yes	Yes	Unclear	No	No

NOS for case-controlled study

Study	Selection	Comparability	Exposure	NOS STARS
Aggarwal et al. (2013)	***	*	**	6

The scale rates the quality of studies by the evaluation of three aspects (i.e. selection, comparability, and exposure), and it allocates a maximum of nine stars for the highest quality

The checklist ascertains the presence of several methodological aspects through a four-response scoring (i.e. yes, no, unclear, not applicable)

NOS Newcastle Ottawa Scale, *JBI* Joanna Briggs Institute Critical Appraisal Checklist for Case Reports

the diagnosis of idiopathic HPT was not clearly highlighted. The authors discussed the case of a 70-year-old woman referred to hospital due to stiffness in the upper extremities; contextually, a cognitive assessment as well as laboratory and radiological investigations revealed the presence of cognitive impairment and clinical signs of idiopathic HPT, respectively [35]. This temporal relationship was substantially consistent across those cases of secondary HPT (i.e. postsurgical), since the thyroidectomy was undergone from 24 to 43 years earlier, followed by the consequent occurrence of progressive cognitive disturbances.

The employment of validated test and batteries to assess cognitive functions was present in six studies [23–25, 29, 33, 35]; specifically, global cognitive functioning was assessed through the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA); the Wechsler Adult Intelligence Scale (WAIS) was used to evaluate patient's IQ; neuropsychological batteries allowed to measure different cognitive functions, such as memory, attention, abstract thinking, executive functions, and visuomotor coordination. In the remaining case reports, cognitive symptoms were solely described.

Cross sectional controlled study

The cross-sectional controlled study [37] involved 62 patients with idiopathic HPT (mean age 36.6 ± 15.16 years) attending the Endocrine Unit, and seventy controls (mean age 37.4 ± 15.22 years) who were unaffected attendants of admitted patients of various endocrine diseases, and who showed normal serum total calcium and phosphorus levels. The employed statistical approach consisted of computing Student's *t* test and Wilcoxon test to describe differences between patients and controls; furthermore, multiple regression was performed, considering the presence of neuropsychological dysfunction among patients with idiopathic HPT as the dependent variable.

A trained psychologist carried out the neuropsychological evaluation through a battery of standard tests, assessing global cognitive functioning, orientation, visual attention, psychomotor speed, letter–number switching, verbal and visual memory, visuo-spatial abilities, response inhibition and intelligence quotient. A global cognitive dysfunction score was then calculated by combining the observed impairment in each administered test, which was scored as '1' when impaired and '0' if normal.

The mean serum total calcium among patients, measured at the time of the neuropsychological assessment, was 7.7 ± 1.20 mg %. CT scans were performed and to detect the presence of brain calcification (basal ganglia, thalamus, cerebellum, dentate nucleus and periventricular region).

Aggarwal and colleagues highlighted that a significant proportion of patients with idiopathic HPT, compared to

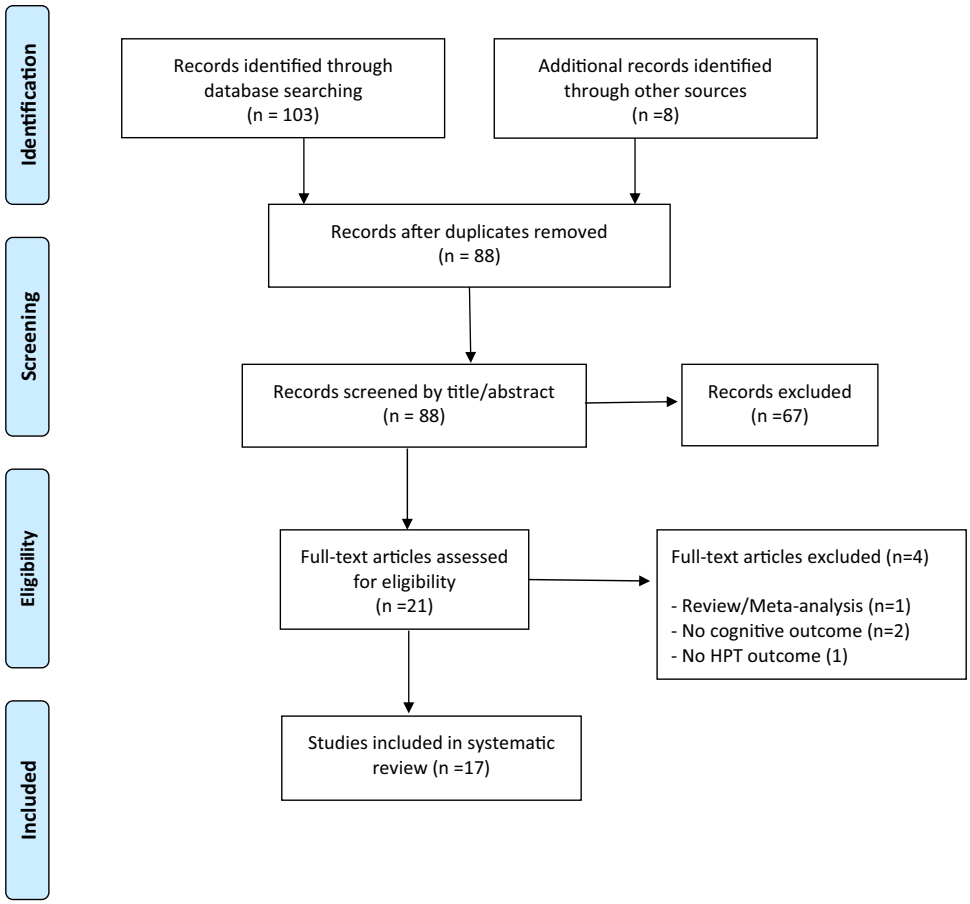

Fig. 1 PRISMA Flow Diagram

controls, was more cognitively impaired [32.3% (95% CI 20.9–45.3) vs 5.7% (95% CI 1.6–14.0), $p < 0.001$]. Among patients, cognitive dysfunction score was significantly lower by 1.7 points in males ($p = 0.02$). Moreover, cognitive dysfunction score was significantly increased by 0.21 for each year increase in the duration of illness ($p = 0.001$) and by 5.5 for one unit increase in serum calcium–phosphorus product ($p = 0.01$), and eventually, the cognitive scores improved by 0.27 for every mg% increase in serum total calcium ($p = 0.001$).

According to the study findings, serum total calcium and its product with phosphorus were discussed as independent predictors of neuropsychological dysfunctions; conversely, intracranial calcifications resulted not significantly associated to the severity of cognitive impairment. Furthermore, Aggarwal and colleagues revealed several peculiar cognitive deficits not frequently reported, such as psychomotor retardation, reduced inhibitory control, impairment in visuo-spatial functioning, constructive apraxia and micrographic writing.

Discussion

The purpose of the present review was to systematically summarize the available evidence accounting the association between cognitive impairment and HPT. To the best of our knowledge, this contribution represents the first attempt to provide an updated state of the art on this topic.

As above mentioned, the presence of intracranial calcifications is a common finding in HPT. The calcifications are usually sited in the basal ganglia region involving lenticular and caudate nuclei, and spread to further brain areas, such as thalamus, cerebellum. Particularly, Goswami et al. [38] have quantitatively assessed the extent of calcifications within the basal ganglia obtained from 93 head computed tomography scans in patients with idiopathic HPT. The lentiform nucleus, representing putamen and globus pallidus, and caudate nuclei were the most commonly affected (69%, 56% and 55%, respectively); furthermore, the gray–white matter junction (40%), cerebellar

Table 2 Main characteristics of the included studies (chronologically listed)

	Study design participants	Cognitive assessment	Main findings
Robinson et al. (1954)	Case report ♀ 61 years	Not detailed	The patient had a history of epilepsy (onset about seven years earlier); a progressive memory decline and confusion over the past five weeks was referred. The cognitive evaluation evidenced disorientation and concentration deficit. X-ray examination evidenced basal ganglia calcifications. Treatment with intravenous calcium gluconate and dihydrotachysterol was started; over the following weeks cognitive functions progressively improved Idiopathic hypoparathyroidism associated with dementia was diagnosed
Eraut (1974)	Case report ♂ 80 years	Descriptive	The patient was observed following a fall at home. Idiopathic hypoparathyroidism was associated to spatial–temporal disorientation, mental confusion and irritability The cognitive profile progressively improved after treatment by intravenous calcium and dihydrotachysterol
Mateo and Gimenez-Roldan (1982)	Case report ♂ 33 years	WAIS scale for IQ	The patient suffered from epileptic episodes and presented a 3-year history of cognitive decline (forgetfulness, confusion, loss of daily autonomy) confirmed by progressive impairment measured by the WAIS scale for both verbal and performance IQ Idiopathic hypoparathyroidism was diagnosed. Alfacalcidol was administered (1 mg oral dose); oral calcium supplement (4 gr carbonate daily) was also given. A progressive improvement of cognitive performances (followed-up by WAIS scale administration) was detected
Lorusso et al. (1994)	Case report ♂ 64 years	Mini deterioration battery (MDB)	The patient was observed following a tonic–clonic seizure. A 10-year earlier progressive decline of memory was referred. CT scan showed massive intracerebral calcifications Cognitive assessment was performed after 15 days from admission: impairment in temporal orientation, verbal and visual memory, attention, and verbal analogies were detected. Calcium carbonate (3 g/day) and dihydrotachysterol (1 mg/die) were administered Idiopathic hypoparathyroidism was diagnosed; a global cognitive functions improvement was detected on a six-month follow-up and on a 3-year follow-up (especially for memory and attention)

Table 2 (continued)

	Study design participants	Cognitive assessment	Main findings
Nicolai, Lazzarino (1994)	Case report Patient 1: ♀ 67 years Patients 2: ♀ 62 years	Neuropsychological battery	Patient 1 with history of thyroidectomy for goiter (24 years earlier) was admitted due to cognitive decline progressively worsened in the last 10 years (confusion, memory impairment, behavioral disturbances) Patients 2 with history of thyroidectomy for goiter (30 years earlier) was admitted due to cognitive decline progressively worsened in the last 10 years (confusion, memory impairment, problem-solving deficit, behavioral disturbances) Both the CT scans revealed intracranial calcifications; In Patient 1, SPECT revealed bilateral frontal, parietal and temporal hypoperfusion. In Patient 2, SPECT revealed frontal and parietal hypoperfusion MMSE, Stroop Test, WCST, BNT, Digit Span were administered to both patients. The neuropsychological assessment detected impairment in memory, attention, abstract thinking, in patient 1, and abstract thinking and memory in patient 2 Cognitive impairment following postsurgical hypoparathyroidism was diagnosed in both patients. The treatment with dihydrotachysterol and calcium carbonate was beneficial only for calcium levels (cognitive impairment persisted a year after the discharge in patient 1, and after 6 months in patient 2)
Roca et al. (1995)	Case report ♂ 61 years	Descriptive	The patient was admitted due to uncontrollable seizures; progressive cognitive decline and loss of daily autonomy in the last two years were referred. CT scans revealed subcortical calcifications. Cognitive evaluation showed incoherence and apathy Idiopathic hypoparathyroidism was diagnosed. Oral calcium and Vitamin D were administered, associated with a moderate (not fully, though) cognitive improvement in the following weeks

Table 2 (continued)

	Study design participants	Cognitive assessment	Main findings
Stueremburg et al. (1996)	Case report ♂ 51 years	Descriptive	The patient was admitted due to a decline of cognitive functions progressively worsened in the last weeks (confusion, disorientation and inappropriate behaviors). Laboratory test showed normal calcium levels, and reduced parathormone, 25-hydroxy-cholecalciferol and 1.25-dihydroxy-cholecalciferol levels CT scan revealed no intracranial calcifications. Mental and cognitive evaluation revealed disorientation, visual-motor disorganization, sensory aphasia, and fluctuating consciousness. Idiopathic hypoparathyroidism (without hypocalcaemia) was diagnosed 1.25-Dihydroxy-cholecalciferol was administered (2 mcg/day for 16 days; then, 0.25 mcg/day). Cognitive performances globally improved and substantially normalized at 1-year follow-up The cognitive impairment due to hypoparathyroidism was justified by the presence of low parathormone, low 25-hydroxy-cholecalciferol and low 1.25-dihydroxy-cholecalciferol levels. Bilateral cataracts and rigidity were considered signs of hypoparathyroidisms. The Authors suggest for the first time that hypocalcaemia might not be the sole cause of dementia in idiopathic hypoparathyroidism
Galvez-Jimenez et al. (2000)	Case report ♀ 74 years	Descriptive	The patient was admitted due to progressive cognitive impairment and movement disturbances. A thyroidectomy for a thyroid adenoma 30 years earlier was referred. A progressive decline of memory and behavioral disturbances were referred. Neurorimaging revealed subcortical calcifications, and hypometabolic intake in the frontal, parietal and temporal regions. Cognitive evaluation showed disorientation, attention deficit, and ideomotor apraxia Postsurgical hypoparathyroidism was diagnosed, associated with progressive dementia, dyspraxia, parkinsonism, oculomotor disturbances, and chorea. The patient started a treatment with vitamin D and calcium supplementation, with no benefit for cognitive performances after 14-month follow-up

Table 2 (continued)

	Study design participants	Cognitive assessment	Main findings
Heckmann et al. (2000)	Case report ♀ 66 years	MMSE	The patient was admitted due to progressive cognitive impairment, inability to walk, and finally stupor. The patient underwent a thyroidectomy 43 years earlier for goiter. Laboratory tests revealed hypercalcemia and decreased parathyroid hormone. CT scans showed extensive intracranial calcifications Further inquiries revealed that the patient was treated for hypocalcaemia episodes with calcium carbonate (900 mg daily) and dihydrotachysterol (1·5 mg daily) 2 months before admission Secondary hypoparathyroidism was not diagnosed until nearly 43 years after thyroidectomy. Reversible hyper- calcaemic dementia was a result of hypoparathyroidism with drug overdosage
Adorni et al. (2005)	Case report ♀ 72 years	Not detailed	The patients underwent a total thyroidectomy 41 years earlier, followed by progressive cognitive decline, behavioral and mood disturbances. Extensive intracranial calcifications were found through CT scans Cognitive impairment due to postsurgical hypoparathyroidism was diagnosed
Titlic et al. (2008)	Case report ♂ 46 years	Descriptive	The patient was admitted due to tonic clonic seizures. A progressive cognitive decline over the past two years was referred. CT scans evidenced intracranial calcifications. Cognitive evaluation indicated a marked impairment involving abstract thinking, planning and flexibility; additionally, a memory deficit in learning and recalling was detected. A treatment with calcium and vitamin D supplementation was started, followed by a general cognitive improvement. Idiopathic hypoparathyroidism was associated to progressive cognitive impairment
Katsidzira et al. (2010)	Case report ♀ 77 years	Not detailed	The patient referred a 4-month history of progressive memory decline and confusion; she developed also visual and auditory hallucinations. CT scans evidenced symmetric intracranial calcifications. Idiopathic hypoparathyroidism associated to cognitive impairment was diagnosed
Aggarwal et al. (2013)	Cross-sectional Idiopathic hypoparathyroidism patients ($n=62$) Control subjects ($n=70$)	Neuropsychological battery	Patients were attending the Endocrine Unit; idiopathic hypoparathyroidism (IH) was diagnosed. A comprehensive neuropsychological evaluation was performed (MMSE, attention, memory, executive functions, frontal tasks, visual constructive abilities) A significantly higher proportion (32.3%) of patients with IH showed neuropsychological dysfunctions than controls (5.7%). Neuropsychological dysfunctions correlated with duration of illness, female gender, serum calcium and calcium–phosphorus, but not with intracranial calcifications

Table 2 (continued)

	Study design participants	Cognitive assessment	Main findings
Kumar et al. (2013)	Case report ♂ 25 years	MoCA Neuropsychological battery	The patient referred mental confusion, forgetfulness, decreased attention, impaired planning, and decision making from the past 2 years. CT scans evidenced bilateral symmetrical subcortical calcifications. Cognitive evaluation detected deficits in attention, working memory, inhibition, short-term and delayed verbal memory and visuomotor coordination. Idiopathic hypoparathyroidism associated to cognitive impairment was diagnosed. A treatment with calcium and vitamin D supplementation was started
Moreno et al. (2015)	Case report ♀ 57 years	Not detailed	The patient was diagnosed 17 years earlier with Idiopathic hypoparathyroidism (IH) and Systemic sclerosis (SS). The patient was observed for motor disturbances, memory loss and behavioral changes over the previous year. CT scans revealed multiple bilateral, symmetrical intracerebral calcification. Treatment with calcium, magnesium, and 25-OH vitamin D was started. A further neurological study, including an examination of cerebrospinal fluid, contribute to a diagnosis of cortical-subcortical mild to moderate dementia. A diagnosis of Fahr's Disease associated with IH was disclosed
Terada et al. (2015)	Case report ♀ 70 years	Neuropsychological battery	The patients referred to the hospital for progressive stiffness in the upper extremities. CT scans evidenced remarkable calcification in the basal ganglia, thalamus, and dentate nuclei. PET study revealed frontal, temporal and parietal hypometabolism. Neuropsychological evaluation evidenced a general cognitive impairment (measured by the WAIS verbal and performance IQ) associated with deficits in delayed recall, attention and frontal functioning (perseverations). Idiopathic hypoparathyroidism associated to cognitive impairment was diagnosed, additionally witnessed by PET imaging
Dos Santos et al. (2016)	Case report ♀ 76 years	Not detailed	The patient was admitted due to generalized tonic clonic seizures. She underwent a total thyroidectomy for goiter 30 years before. Further antecedents were progressive cognitive impairment and mood changes. CT scans evidenced multiple intracranial bilateral calcifications. A therapy with intravenous calcium gluconate was started, followed by general cognitive improvements. Fahr's syndrome and postsurgical hypoparathyroidism was diagnosed

MMSE Mini Mental State Examination, *MoCA* Montreal Cognitive Assessment, *BNT* Boston Naming Test, *WCST* Wisconsin Card Sorting Test, *WAIS* Wechsler Adult Intelligence Scale

parenchyma and dentate nucleus (32% and 24%, respectively), and thalamus (24%) were consistently associated with basal ganglia calcifications. Choroid plexus calcification was mainly observed in subjects with basal ganglia calcifications at baseline, and in those who showed progression. The occurrence and progression of calcification have been associated with the duration of disease and the calcium/phosphorus ratio [38, 39].

Noteworthy, basal ganglia calcifications are found frequently in renal replacement therapy patients with HPT, while in uremic patients with increased PTH, these calcifications are extremely rare, thus possibly implying a PTH-mediated protective mechanism against basal ganglia and intracerebral calcifications [40]. As recently suggested, in HPT patients, the lack of PTH signaling, hypocalcemia and hyperphosphatemia promote calcium–phosphate deposition, mainly in the extracellular space of basal ganglia. In fact, the sodium-dependent phosphate transporter 2 and carbonic anhydrase-II could be directly affected by the lack of PTH, leading to enhanced phosphate concentrations in the extracellular space and to inadequate degree of acidification and finally to phosphate and calcium precipitation [40].

The strict clinical meaning of the basal ganglia calcifications in HPT is still not clear. Brain calcifications have been associated with neurological dysfunctions including decreased attention, memory, information processing, executive functions and extrapyramidal symptoms. Nonetheless, nor number, volume and sites of intracranial calcifications were consistently associated with neuropsychological, extrapyramidal and cerebellar dysfunctions in the study by Aggarwal and colleagues [37] as they considered young patients while neurological dysfunction might show an association with intracranial calcification with advancing age. These neurologic dysfunctions could be due to the disruption of the corticostriatal tract carrying sensory input from cerebral cortex to striatum (caudate and putamen), finally relaying to globus pallidus, which tunes the sensory input along with dentate-thalamic tract and projects the signals back to the cortex for organized activities [41]. Besides, intracranial calcifications site may differently affect cognitive functions, since calcification occurring predominantly in the perivascular region or synaptic regions of the corticospinal tracts could result in impaired blood flow with secondary hypoxia and impaired dopamine and glutamate transmissions.

Interestingly, in the study by Aggarwal and colleagues, a multiple regression analysis identified serum total calcium and the calcium product with phosphorus as independent predictors of neuropsychological dysfunction [37]. Hypocalcemia may exacerbate the neurological dysfunction induced by cerebral calcifications; furthermore, pharmacological correction of serum calcium levels with calcium supplements and active vitamin D may lead to a partial improvement of neuromotor symptoms. On the other hand, exogenous PTH (1–84) administration in patients with HPT has been shown to improve, but not normalize, physical and mental well-being, and this may depend at least in part by the time of pharmacological intervention [16].

Although many of the neurological features in HPT have been considered to be linked to brain calcifications and hypocalcemia, the role of PTH receptor should be additionally taken into consideration. Particularly, the PTH 2 receptor (PTH2R) is a member of the Family B group of G protein-coupled receptors (GPCRs), distributed in both the central nervous system and different peripheral organs [42]. At central level, it is mainly expressed in the amygdala, medial preoptic area, hypothalamic paraventricular and periventricular nuclei, medial geniculate, and the pontine tegmentum. The distribution of PTH2R-immunoreactive fibers includes dense fiber network in the medial preoptic area, hypothalamic paraventricular, periventricular and infundibular (arcuate) nuclei, lateral hypothalamic area, median eminence, thalamic paraventricular nucleus, periaqueductal gray, lateral parabrachial nucleus, nucleus of the solitary tract, sensory trigeminal nuclei, medullary dorsal reticular nucleus, and dorsal horn of the spinal cord. Besides, PTH2R is also expressed by endocrine cells that include pancreatic islet somatostatin cells, thyroid parafollicular cells, and peptide secreting cells in the gastrointestinal tract, and by cells in the vasculature and heart. According to the central expression of PTH2R, it has been suggested this receptor may participate in neuroendocrine, limbic and sensory processing functions [43].

An additional element of scientific interest has widely considered the tuber infundibular peptide of 39 residues (TIP39), which has been originally purified and sequenced two decades ago, and which is acknowledged as a strong and selective natural agonist of the PTH2R [42, 44]. In this context, the brain expression of TIP39 has been recently detected in the subparafascicular region in the posterior thalamus, and the medial paralemniscal nucleus in the lateral pons [45].

Since the axon terminals of TIP39 neurons result distributed similarly as the PTH2R containing neurons, the implications of the joint TIP39-PTH2R system in nociceptive information processing in the spinal cord, in the regulation of different hypophysiotropic neurons in the hypothalamus, and in the modulation of emotional processes have been suggested. Accordingly, TIP39-KO mice demonstrated memory impairment selectively under conditions of novelty-induced arousal. Acute administration of a PTH2R antagonist in wild-type mice had a similar effect [46].

Although stimulation of PTH2R by TIP39 results in a twofold greater accumulation in cAMP than that elicited by PTH, and TIP39 is considered 100-fold more potent than PTH, it could be speculated that pathological alteration of

serum PTH may lead to neuropsychological consequences also via PTH2R [44].

There is a lack of data on the ability of replacement therapy with PTH or its analogues, which are also able to restore the calcium product with phosphorus closer to normal, to significantly modify the progression of cerebral calcifications and cognitive clues in HPT [17, 47–49]. A further relevant point not deeply accounted among the retrieved studies is the potential impact on the onset and the maintenance of cognitive dysfunctions of the disease control by conventional therapy, since a poor control might be associated to the progression of cognitive impairment.

Despite the topic is worthy of interest, HPT is a rare disease and the overall available evidences on the association between cognitive dysfunctions and HPT are principally limited to case reports [13, 50]. Only one cross-sectional controlled study investigating cognitive profile among patients with idiopathic HPT was retrieved [37]; the overall quality of the study was fair according to the NOS score, with the main uncertainty regarding the selection criteria of the control group, which was unclear even though the control group was classified as healthy. The overall quality of case reports was evaluated through the JBI Critical Appraisal Checklist for Case Reports; the mean quality score was 4.37/8 (with scores ranging from 1/8 to 6/8). The description of patients' sociodemographic characteristics was quite limited across the studies, since age and gender were the only factors constantly accounted in each report. No case report highlighted the occurrence of adverse effects. Anamnestic information regarding the patients' medical history was collected and clearly described in the majority of the studies; only four studies reported unclear or vague anamnestic information. Additionally, the description of post-treatment clinical conditions was not sufficiently clear (seven studies), or it was substantially missing (three studies) in the majority of the reports. Conversely, the presentation of the patients' current clinical condition, the description of diagnostic tests or assessment methods, and the description of the treatment procedures were more accurate. However, with regard to the description of the assessment methods, a further qualitative limitation should be additionally highlighted, since the description of the performed cognitive assessment often resulted vague, and it was not always clear whether or which assessment tool was administered.

In conclusion, the aim of the current systematic review was to provide an updated state-of-the-art concerning the association between cognitive impairment and HPT. Even though mostly based on single case reports, the presence of neuropsychological dysfunctions in the context of HPT appears to be a consistent core finding. Further longitudinal studies are strongly recommended to better understand the cognitive profile of subjects with HPT; consistently, the employment of standardized neuropsychological batteries might facilitate a better generalizability of the evidence, making them much more easily comparable. Similarly, future studies on this topic should additionally account the impact of the patients' adherence to therapy as a potential risk factor for the progression of cognitive dysfunctions.

The presence of progressive cognitive disturbances is a core finding of aging. In this context, the investigation of potential modifiable risk factors related to cognitive impairment has gained interest increasingly over the past years [51]. Consistently, accounting the early occurrence of cognitive dysfunctions in subjects with HPT could allow physicians to more comprehensively acknowledge the wide symptomatology of HPT, as well as to better observe patients' cognitive trajectories potentially leading to dementia. In this perspective, it could be useful, both as a challenging novel research topic and in clinical practice, to address those patients with HPT, who may exhibit early cognitive disturbances, to cognitive stimulation interventions aimed at improving cognitive reserves, following in parallel the evolution of both cognitive and disease-related symptomatology.

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