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Could hyperlipidemia be a risk factor for corticobasal syndrome? — a pilot study

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ABSTRACT

Introduction. Corticobasal syndrome (CBS) is a specific clinical manifestation shared by multiple pathologies. The exact mechanism of this phenomenon remains unclear. Differential diagnosis of CBS in everyday clinical practice is challenging, as this syndrome can overlap with other entities, especially progressive supranuclear palsy Richardson-Steele phenotype (PSP-RS). Several papers have suggested a possible role of vascular pathology as a linking factor in the pathogenesis of CBS based on different neuropathologies. This paper analyses differences in the occurrence of the most common vascular risk factors such as hypertension and lipid profile with respect to dietary habits among patients who fulfill the diagnostic criteria for probable/possible CBS and PSP-RS.

Material and methods. Seventy (70) patients in total were included in the study. Exclusion criteria comprised hydrocephalus, stroke in the past, the presence of marked vascular changes in white matter defined as the presence of vascular change ≥ 1 mm in 3T MRI, medical history of hyperlipidemia or the use of drugs that could impact upon lipid metabolism before the initiation of the neurodegenerative disease, and neoplastic focuses in the central nervous system. Patients with diabetes, or with BMI exceeding 18–25, or who were smokers, or who were affected by chronic stress were also excluded. Data was analysed statistically using the Shapiro-Wilk test, the U Mann-Whitney test for group comparison, and a Bonferroni correction to control the false discovery rate (FDR).

Results. Our obtained results indicated a statistically significantly higher level of total cholesterol in the CBS group ($p = 0.0039$) without a correlation with dietary habits.

Conclusions and clinical implications. The results obtained in our study may suggest a possible role of vascular pathology in CBS development. This issue requires further research.

Key words: corticobasal syndrome, hyperlipidemia, neurodegeneration, risk factor, CBS phenotype

Introduction

Corticobasal syndrome (CBS) is a complex of clinical symptoms highly diversified when it comes to underlying pathology. According to the recent criteria of diagnosis, it is associated with "asymmetric manifestation of limb rigidity, akinesia, limb dystonia, limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit and alien limb phenomenon" [1]. Progressive supranuclear palsy is the most common atypical parkinsonism. The most common phenotype is Richardson syndrome, which is associated with oculomotor and postural instability [2]. Both these diseases are referred to as

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atypical parkinsonian syndromes. Historically, CBS has been associated with four-repeats tau pathology, otherwise known as corticobasal degeneration (CBD). With the progress in the assessment of CBS, it has been established that this clinical manifestation is related to up to half of the cases of CBD [1, 3]. CBD may also manifest as progressive supranuclear palsy syndrome (PSPS), frontotemporal dementia, Alzheimer's- like dementia, frontal behavioural-spatial syndrome or non-fluent/agrammatic variant of primary progressive aphasia [4]. The more precise assessment of CBS patients has shown that although CBD is a major pathology of CBS, it is not the only one. Post mortem examinations of other patients have revealed a surprisingly high incidence of CBS manifestations with multiple types of underlying pathologies. Examples include progressive supranuclear palsy (PSP), Pick's disease, Lewy body disease, TDP43 type A, Creutzfeldt–Jakob disease, globular glial tauopathy and Alzheimer's disease [5]. The literature has also associated CBS with pathologies based on vascular changes [3].

Despite the complicated correlation between clinical manifestation and its pathology, the main obstacle to correct diagnosis is related to overlapping clinical manifestations between CBS and other tauopathic parkinsonian syndromes, especially progressive supranuclear palsy syndromes [6]. Currently CBS is interpreted as a group of pathologies linked by the same clinical manifestation. The exact mechanism leading to a concurrent syndrome despite multiple pathologies remains unclear.

Clinical rationale for study

The most common phenotype of PSPS is PSP-Richardson Syndrome (PSP-RS), which in the vast majority of cases is related to PSP pathology [6]. The overlaps and often unclear boundaries between PSPS and CBS cause difficulties in obtaining a proper diagnosis using a clinical assessment. Among these overlaps are bradykinesia, cognitive deterioration, changes of behaviour, and postural instability [1, 2]. This has led to the introduction of a probable 4-repeat (4R)-tauopathy diagnosis [7], which combines CBD and PSP into one clinical entity.

The latest literature highlights the importance of vascular pathology in CBS development [5]. Assuming this hypothesis to be true, the aim of this study was to verify whether patients who fulfill the current diagnostic criteria for CBS diagnosis differ from patients with PSP-RS in the context of dyslipidemia severity, which is a known vascular risk factor.

Material and methods

Seventy (70) patients with atypical parkinsonism were included in the study: 51 patients with a clinical diagnosis of PSP-RS (19 females, 32 males) aged 62-83 years and 19 patients (18 females, one male) with CBS aged 57 to 87. The disease duration among all patients varied from 3 to 6 years. The clinical diagnosis was based on the recent criteria of diagnosis of PSP and CBS [1, 2]. All of the clinical examinations were performed by neurologists experienced in movement disorders between January 2017 and December 2021 in the Departments of Neurology in Warsaw and Prague. Excluded from our study were patients with hydrocephalus, who had undergone stroke, with marked vascular changes in white matter defined as presence of vascular change ≥ 1 mm, with a medical history of hyperlipidemia or the use of drugs that could impact upon lipid metabolism before the initiation of the neurodegenerative disease, and neoplastic focuses in the central nervous system. Patients with diabetes, or BMI exceeding 18–25, or who were smokers, or who were affected by chronic stress were also excluded.

Analysed data included lipid profile, presence of hypertension, and a nutrition survey of patients and caregivers involved in food preparation. This survey covered all foods consumed by the patient on three consecutive days, taking into account the portion size. On this basis, the average daily amount of kilocalories and the nutritional values taken by the patient were calculated.

The study was approved by the Bioethical Commission of the Medical University of Warsaw (AKBE/209/2021).

Laboratory testing

All of the patients included in the study underwent biochemical analysis of blood samples. The evaluation was conducted during hospitalisation in the Departments of Neurology in Warsaw or Prague. The analysis of blood samples was performed using Sysmex XT 4000i. The evaluated parameters — total cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL) — were assessed automatically and compared to the hospital database of healthy volunteers.

Statistical analysis

All analysis was performed using Statistica software (version 13.1 Statsoft). Data distribution was assessed with Shapiro-Wilk test. Due to non-normal distribution, all parameters are expressed as medians (Me) with a lower (Q1) and an upper (Q3) quartile and their interquartile range (Q1–Q3). For group comparison, we used U Mann-Whitney test. Significant results are presented as box plots. We have provided a scatterplot if necessary. For a final decision with regard to statistical significance we have used corrected p-value after Bonferroni correction to control the False Discovery Rate (FDR). A calculated p value of 0.005 was considered significant.

Results

Hypertension defined as blood pressure > 140/90 mmHg was present in 76.5% of CBS and 43.6% of PSP–RS patients.

Table 1 sets out descriptive statistics for analysed groups of patients with CBS and PSP-RS; median values, Q1, Q3 and Q1–Q3 are given.

Table 1. Descriptive statistics

Parameters	CBS (N = 19) (F/M=18/1)				PSP (N = 51) (F/M = 19/32)			
	Me	Q1	Q3	Q1–Q3	Me	Q1	Q3	Q1–Q3
Lipid parameters								
Total cholesterol	213.0	197.0	239.0	42.0	179.0	160.0	205.0	45.0
HDL	47.0	42.0	55.0	13.0	50.0	39.0	58.0	19.0
LDL	128.0	88.0	154.0	66.0	104.5	86.0	136.0	50.0
TAG	95.0	87.0	107.0	20.0	98.0	77.0	117.0	40.0
Nutrition survey								
Kcal	1,800.0	1,750.0	1,835.0	85.0	1,935.0	1,825.0	2,100.0	275.0
Fat [g]	77.0	75.0	82.5	7.5	81.5	76.0	84.0	8.0
Cholesterol [mg]	225.0	206.5	242.5	36.0	248.0	200.0	279.0	79.0
Carbohydrates [g]	265.0	256.2	272.5	16.4	272.0	257.5	277.5	20.0
Protein [g]	83.8	83.0	85.6	2.6	84.3	83.0	87.0	4.0
Fibre [g]	27.0	25.0	28.0	3.0	27.0	24.0	28.4	4.4

CBS — corticobasal syndrome; HDL — high density lipoprotein; LDL — low density lipoprotein; Me — median; PSP— progressive supranuclear palsy; TAG - triglycerides; Q1 — lower quartile; Q3 — upper quartile; Q1–Q3 — interquartile range

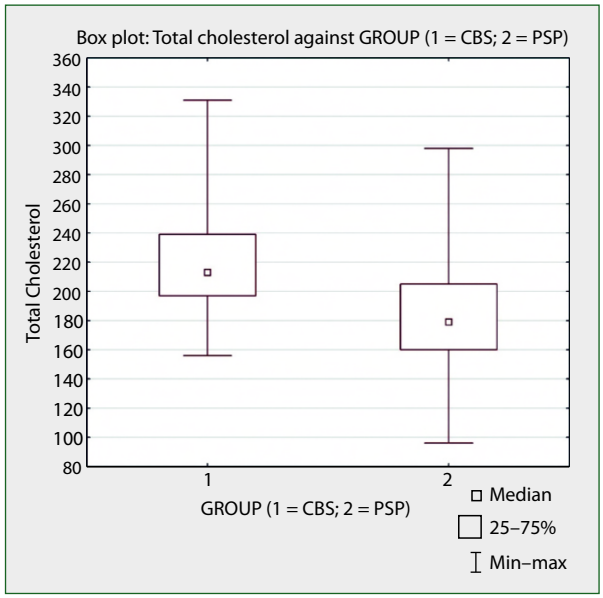

Figure 1. Comparison of median value of total cholesterol between groups

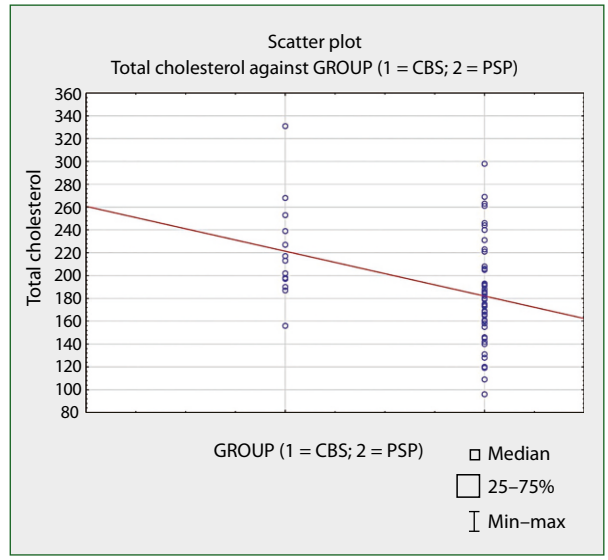

Figure 2. Scatter plot — data distribution in regard to medians differences

Median value of total cholesterol was significantly higher for CBS patients compared to PSP-RS patients: 213.0 *vs.* 179.0 (Fig. 1) Scatter plot also shows adequate data distribution in regard to differences in medians (Fig. 2).

Differences in median values in the rest of the analysed lipid parameters: high-density lipoprotein, low-density lipoprotein, and triacyl glycerides, in CBS and PSP-RS patients, were insignificant $p > 0.005$ (Tab. 2).

Comparison of data from the nutrition survey revealed that only the median value of total calories consumed per day differed between CBS and PSP-RS patients, and was higher in the PSP-RS group compared to CBS patients (1,935 *vs.* 1,800 kilocalories, $p = 0.0005$) (Tab. 2, Fig. 3). This could be at least partly explained by the gender inequality among the groups, with a strong female predominance in CBS.

Differences in other nutrients such as fat, cholesterol, carbohydrates, protein and fibre intake were insignificant (Tab. 2).

Discussion

Our study was affected by several limitations, most notably the lack of neuropathological examination and the screening method of lipid profile assessment, without evaluation of

Table 2. Group analysis in regard of lipid parameters and nutrition survey

Parameters	P-value for UMW test
Lipid parameters	
Total cholesterol	0.0039
HDL	0.6807
LDL	0.2101
TAG	0.9756
Nutrition survey	
Kcal	0.0005
Fat [g]	0.3410
Cholesterol [mg]	0.2041
Carbohydrates [g]	0.1653
Fibre [g]	0.9566
Protein [g]	0.3886

UMW — U Mann-Whitney test

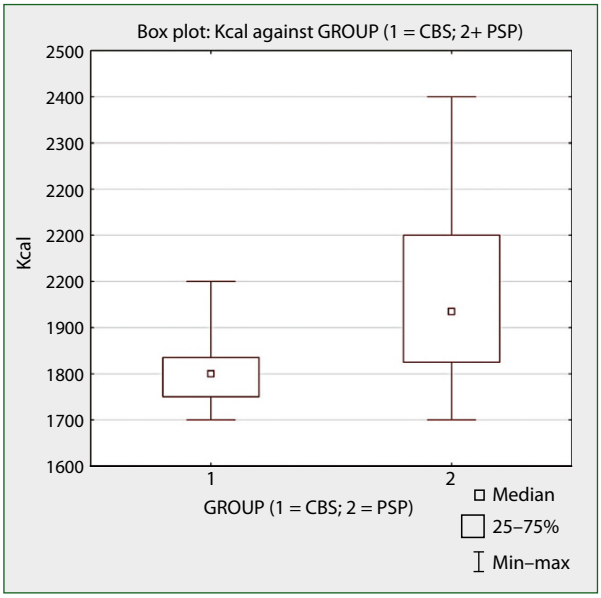

Figure 3. Comparison of data from nutritional survey

specific metabolism pathways, and an unequal representation of male and female patients in the PSP-RS and CBS groups, which is related to the rarity of these diseases.

However, the obtained results suggest that corticobasal syndrome may be more associated with abnormalities in the lipidic parameters than other entities. This, taking into account the fact that the cases were not verified pathologically, may reveal a possible link between vascular pathogenesis commonly described in the literature regarding corticobasal syndrome. Due to the fact that we excluded patients with vascular changes found in magnetic resonance imaging — 3T, the mechanisms may be connected also with abnormalities not evidenced in macroscopic examination.

CBS is one of the entities which are most diversified in the context of pathology, which may suggest an alternative mechanism of syndrome development [1, 3, 4]. The multiple pathologies that are likely to be associated with CBS could impact upon the results related to vascular pathogenesis in this group. In PSP-RS, about 90% cases are related to PSP pathology [8]. In CBS, our knowledge concerning the pathology is still evolving. The fact that an association between CBS and CBD is found in about 50% of cases is relatively well known. However, recent papers have shown that CBS, though associated with tauopathic pathology, may be related to vascular and Lewy body pathogenesis [9, 10] . In our work, patients with ischaemic or haemorrhagic lesions possibly detected using the resolution of MRI were excluded from the study. This issue may suggest the need to search for molecular mechanisms affecting more pronounced dyslipidemia in CBS. A cross-sectional analysis of cardiovascular risk factors and their associations with different neurodegenerative diseases indicates that this association may be restricted to AD pathology [11]; however, corticobasal syndrome often is its clinical presentation.

The association between parkinsonisms and vascular changes has been studied in various clinical entities, although in CBS it has been relatively sparingly described [12]. From the initial definition of CBS right up until today, the interpretation of the disease has continued to evolve. Currently growing interest is associated with the vascular and metabolic pathogeneses of CBS [13]. A postmortem analysis performed on 217 subjects with antemortem diagnosis of CBS revealed three patients with vascular changes [10]. Another work presented a case report of a patient with superior sagittal sinus intracranial dural arteriovenous fistula mimicking corticobasal syndrome [14]. CBS has also been described in patients with multiple ischaemic lesions [15]. The descriptions of vascular pathogenesis are generally based on relatively small numbers of patients or case reports. Hypertension is considered as a significant co-existing and preceding state in the pathogenesis of CBS and related disorders such as PSP [16]. A case report presenting a progressive course of typical CBS symptoms showed disseminated ischaemic lesions and steno-occlusion of both middle cerebral arteries [17]. The explanation for CBS's clinical manifestations requires further research.

Most papers concerning vascular pathogenesis in the context of neurodegenerative disorder have focused on Alzheimer's disease. In 2020, the Lancet Commission on dementia prevention, intervention, and care published a list of 12 modifiable risk factors for dementia development; four of these (diabetes, hypertension, obesity, and lack of physical activity) can be considered also as vascular risk factors [18]. Dysfunction of the neurovascular unit consisting of the blood–brain barrier endothelium and surrounding smooth muscle cells, microglia, pericytes, and astrocytes, as well as abnormal cerebral bloodflow, are associated with early cognitive decline,

regardless of typically described amyloid and tau accumulation [19]. Blood–brain barrier dysfunction increases vascular impairment, causing amyloid angiopathy due to reduction of amyloid efflux [20]. Progressive vasculopathy impairs microcirculation and leads to hypoperfusion and hypoxia described in AD pathogenesis [21]. Dyslipidemia as a factor contributing to vascular pathology causes oxidative stress and inflammation, which leads to further vascular impairment and forms a vicious circle of damage and neurodegeneration. Animal studies clearly indicate that vascular dysfunction promotes neurodegeneration observed in AD-mice models [22]. The issue of neuroinflammation in tauopathies was also recently discussed in the context of PSP and CBD [23].

AD, as well as other types of dementia, are considered as being possibly correlated with vascular mechanism, although the mechanism of this association is not fully understood [24, 25]. The levels of lipids and lipoproteins were verified in a comparison of patients with AD and vascular dementia. This revealed that AD patients had lower levels of total cholesterol, TG, LDL-C, VLDL-C, Non-HDL-C, and atherosclerosis index, not only when compared to vascular dementia patients with a comparable stage of cognitive deterioration, but also compared to healthy controls [26]. Additionally, the risk of AD was not found to be correlated with familial hypercholesterolemia [27]. Although the data concerning lipidic abnormalities in AD does not indicate a concise correlation with lipidic profile, research concerning dyslipidemia in PSP has shown a correlation of LDL-C/HDL-C ratio with the PSP rating scale and the Geriatric Depression Scale. A general study on risk factors for dementia revealed that LDL is a risk factor for dementia a minimum of 10 years later [28].

Regardless of the presented lipidic profile, AD is considered an entity possibly linked with vascular pathogenesis. One paper associates a connection between maximum systolic pulse energy location and the acceleration of atherosclerosis impacted by age [29]. One theory suggests decreased brain perfusion as a factor inducing beta amyloid accumulation and further evolution to dementia [30]. Furthermore, ApoE, one of the genetic determinants of AD, is considered to be a feature correlated with decreased perfusion [31].

A possible association between lipid metabolic changes and parkinsonism has also been described in the context of Parkinson's disease and deep brain stimulation therapy (DBS) [32]. The authors indicated that the DBS group was characterised by increased BMI and TG levels and decreased HDL-C levels.

Clinical implications/future directions

Our results, though affected by certain limitations, may serve as reference points in the discussion concerning vascular factors leading to CBS phenotype. The lack of significant vascular changes in MRI suggests that the abnormalities may not be captured in macroscopic evaluation. The outcome of this study may be beneficial in the context of future therapies dedicated to certain entities. Our results suggest that research concerning the exact pathogenesis of CBS phenotype requires further development.

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