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Cognitive function in patients with primary adrenal insufficiency (Addison's disease)

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Summary
Background: Patients with primary adrenal insufficiency (AI) need to replace glucocorticoids and mineralocorticoids that act on glucocorticoid (GR) and mineralocorticoid receptors (MR). Both receptors are highly expressed in the hippocampus and are closely associated with cognitive function, which might be impaired by insufficient or increased GR and MR stimulation. However, little is known about cognitive function in patients with AI.
Methods: It was examined whether patients with AI exhibit worse cognitive function compared to sex-, age-, and education-matched controls. Cognitive function (executive function, concentration, verbal memory, visual memory, working memory, and autobiographical memory) was assessed in 30 patients with AI (mean age 52.4 yrs. ±14.4, $n = 21$ women, mean duration of illness 18.2 yrs. ±11.1) and 30 matched controls. We also measured depressive symptoms, body mass index (BMI), and blood pressure.
Results: Patients with AI showed more depressive symptoms, had a greater BMI and lower systolic blood pressure compared to controls. Adjusted analyses controlling for these variables revealed that patients with AI performed significantly worse in verbal learning ($F = 7.8$, $p = .007$). Executive function, concentration, working memory, verbal memory, visuospatial memory, and autobiographical memory did not differ between groups.
Conclusions: No clinically relevant cognitive impairment was found in patients with AI compared to matched controls. Even long-term glucocorticoid and mineralocorticoid substitution over almost two decades appears to have only subtle effects on cognition in patients with AI.

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1. Introduction

Primary adrenal insufficiency (AI) is also called Addison's disease named after Thomas Addison (1793—1860) who was the first to describe the characteristic symptoms of hypocortisolism and hypoaldosteronism. The most frequent cause of AI is autoimmune adrenalitis, other causes include adrenalitis due to infections, infiltration, genetic disorders, medication, operation, thrombosis or adrenal infarction with secondary haemochromatosis (Arlt and Allolio, 2003; Quinkler, 2012). In AI, there is a lack of physiological cortisol and aldosterone production. Therefore, patients need to substitute these hormones predominantly using hydrocortisone and fludrocortisone (also called 9α-fluorohydrocortisone or 9α-fluorocortisol) that act via glucocorticoid (GR) and mineralocorticoid receptors (MR). Symptoms shown by most of the patients with AI include weakness, malaise, weight loss, and dehydration with associated low blood pressure (Bleicken et al., 2010b; Herbert et al., 2006). Due to these unspecific symptoms, AI is often misdiagnosed as psychosomatic or psychiatric conditions like depression, adjustment disorders and anorexia, or as gastroenterological diagnoses like irritable bowel syndrome and chronic enteritis (Bleicken et al., 2010b; Quinkler, 2012). Furthermore, quality of life is severely impaired in patients with AI despite hormone substitution (Bleicken et al., 2008, 2010a; Hahner et al., 2007; Kluger et al., 2014; Løvås et al., 2002, 2003, 2010).

Cognitive dysfunction is likely to contribute to problems regarding social functioning and quality of life in patients with AI. In humans, it is known that very high as well as very low levels of cortisol can have adverse effects on cognitive function (Het et al., 2005; Wingenfeld and Wolf, 2014). In the brain, cortisol acts on both MR and GR (De Kloet, 2014). While MR are predominantly found in the hippocampus and the prefrontal cortex GR are expressed widely across the brain (De Kloet, 2014). Both receptor systems are closely involved in cognitive function (De Kloet, 2014). Therefore, it is plausible that long-term glucocorticoid and mineralocorticoid substitution might affect cognitive function in patients with AI. However, surprisingly few studies have examined cognitive function in patients with AI as compared to matched controls.

Klement et al. (2009) examined the role of glucose infusion on cognitive function in patients with AI ($n = 8$) compared to healthy controls ($n = 8$). They found deficits in attention in patients with AI but no differences in short-term memory. Furthermore, the same authors analyzed the influence of high-calorie glucose-rich food on neuroglycopenic symptoms in patients with AI ($n = 10$) as compared to healthy controls ($n = 10$). They found that patients with AI showed worse attention, which improved after comfort food (Klement et al., 2010). Henry and Thomas (2014) assessed cognitive function in 27 patients with AI compared to 27 matched healthy controls. They measured cognitive function via telephone and found impairment in episodic memory in patients with AI. There were no significant between-group differences in attention, executive functioning, reasoning, and speed of processing.

Based on the evidence from these studies, only limited conclusions can be drawn. The aim of our study was to investigate whether patients with AI show worse cognitive function as compared to age-, sex- and education-matched controls. We hypothesized that patients with AI exhibit worse cognitive function, especially in hippocampus-related cognitive domains.

2. Methods and materials

2.1. Participants

Our sample comprised 30 patients with AI and 30 age-, sex-, and education-matched controls. All patients with AI were recruited from a consecutive sample of the Department of Clinical Endocrinology at the Charité University Medical Center Berlin.

The controls were recruited through local advertisement like postings on websites, hospitals, and other public places. Exclusion criteria included central nervous system diseases and psychiatric diseases, previous traumatic brain injury, malignant tumors, HIV infection, symptomatic cardiac arrhythmias as well as myocardial infarction, unstable hypertension, metabolic disease like type I and type II diabetes mellitus, ingestion of oral and inhalative glucocorticoids (all cortisol containing compounds). The control group was matched with the patient group regarding age, sex and education. Due to the influence of the female cycle and the status of the menopause on the hypothalamic-pituitary-adrenal axis (HPA-axis), female controls were also matched with regard to the phase of the menstrual cycle (follicular vs. luteal) and the status of the menopause.

2.2. Procedures

Patients with AI and matched controls were tested at the same time of day. Testing started in the afternoon between 1 p.m. and 4 p.m. First, the participants completed a psychometrical assessment including measurement of depressive symptoms in the last two weeks (Patient Health Questionnaire, PHQ-9) (Spitzer et al., 1999) and current psychological condition including mood, vigilance-fatigue, composure-restlessness (Multidimensional Mood State Questionnaire, i.e. Mehrdimensionaler Befindlichkeitsfragebogen, MDBF) (Steyer et al., 1997). Fifteen minutes later, blood pressure levels were measured twice with 5 min in between. The subsequent neuropsychological testing lasted 1 h. Afterwards, blood pressure was again measured for the last time. Patients with AI took replacement therapy as prescribed. All study personnel conducting cognitive testing or statistical analyses were blinded to group membership.

2.3. Neuropsychological assessment

Neuropsychological testing comprised the auditory verbal learning test (AVLT), the Rey—Osterrieth complex figure test (ROCF), the Digit Span Task, the Stroop test, the Number-Combination test (''Zahlen-Verbindungs-Test'', ZVT) and the Autobiographical Memory test (AMT).

The AVLT (Helmstaedter and Durwen, 1990) measures verbal learning as well as short-term and long-term verbal memory. In this test, the examiner reads different word lists