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Low serum insulin-like growth factor-I (IGF-I) level is associated with increased risk of vascular dementia

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ABSTRACT

Background: Insulin-like growth factor-I (IGF-I) is important for the adult brain, but little is known of the role of IGF-I in Alzheimer's disease (AD) or vascular dementia (VaD).
Methods: A prospective study of 342 patients with subjective or objective mild cognitive impairment recruited at a single memory clinic. We determined whether serum IGF-I concentrations at baseline were associated with the risk of all-cause dementia, AD, or VaD. Patients developing mixed forms of AD and VaD were defined as suffering from VaD. The statistical analyses included Cox proportional hazards regression analysis.
Results: During the follow-up (mean 3.6 years), 95 (28%) of the patients developed all-cause dementia [AD, n = 37 (11%) and VaD, n = 42 (12%)]. Low as well as high serum IGF-I (quartile 1 or 4 vs. quartiles 2–3) did not associate with all-cause dementia [crude hazard ratio (HR) 1.30, 95% confidence interval (CI): 0.81–2.08 and crude HR 1.05, 95% CI: 0.63–1.75, respectively] or AD (crude HR 0.79, 95% CI: 0.35–1.79 and crude HR 0.94, 95% CI: 0.43–2.06, respectively]. In contrast, low serum IGF-I concentrations were associated with increased risk of VaD (quartile 1 vs. quartiles 2–3, crude HR 2.22, 95% CI: 1.13–4.36). The latter association remained significant also after adjustment for multiple covariates.
Conclusions: In a memory clinic population, low serum IGF-I was a risk marker for subsequent VaD whereas low IGF-I did not associate with the risk of AD. High serum IGF-I was not related to the risk of conversion to dementia.

1. Introduction

Insulin-like growth factor-I (IGF-I) receptors are widely distributed in the central nervous system (CNS). Brain IGF-I can be derived from passage of IGF-I across the blood-brain barrier (Reinhardt and Bondy, 1994), and by local production of IGF-I in the CNS (Rivera et al., 2005). Furthermore, neuronal activity induces transportation of peripheral IGF-I into the CNS (Nishijima et al., 2010).

IGF-I is of vital importance for brain development (Fernandez and Torres-Alemán, 2012), but IGF-I also affects the adult brain. In rodent studies, circulating IGF-I mediated the exercise-induced increase in new neurons in the adult hippocampus (Trejo et al., 2001), regulated the density of blood vessels in the adult brain (Lopez-Lopez et al., 2004), and was associated with spatial learning and memory (Ohlsson et al., 2009; Svensson et al., 2006). Furthermore, dysregulation of IGF-I could also be involved in the pathogenesis of Alzheimer's disease (AD). Deficiency of IGF-I in the brain was associated with hyperphosphorylation of tau (Cheng et al., 2005). Systemic IGF-I treatment increased the clearance of β-amyloid (Aβ), thereby reducing Aβ burden in Tg2576 mice overexpressing a mutant form of human amyloid precursor protein (APP695 KM670/671NL) (Carro et al., 2002).

In humans, IGF-I gene mutations are associated with mental retardation (Ohlsson et al., 2009). A study based on the Framingham cohort displayed that low IGF-I was associated with reduced brain size and increased risk of AD (Westwood et al., 2014). In another epidemiological study based on the Rotterdam cohort (de Bruijn et al., 2014), high IGF-I receptor stimulating activity was associated with increased risk of dementia (de Bruijn et al., 2014). Postmortem studies displayed resistance to IGF-I receptor signaling in the human AD brain (Rivera et al., 2005; Steen et al., 2005; Talbot et al., 2012), which could result in lack of trophic signals with subsequent degeneration of neurons (de la Monte, 2012; Fernandez and Torres-Alemán, 2012). However, in patients with manifest AD, determinations of IGF-I concentrations have shown variable results as circulating or cerebrospinal (CSF) IGF-I levels have been low (Duron et al., 2012; Mustafa et al., 1999; Watanabe et al., 2005), unchanged (Hertze et al., 2014; Johansson et al., 2013; Tham et al., 1993), or increased (Johansson et al., 2013; Salehi et al., 2008; Tham et al., 1993; Vardy et al., 2007) compared to controls. In

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one additional study, low IGF-I was associated with faster cognitive decline in manifest AD (Vidal et al., 2016).

In addition to possibly being involved in AD pathogenesis, low IGF-I is a risk factor for cardiovascular disease (CVD) morbidity. Studies of polymorphisms in the IGF-I gene demonstrated a link between low serum IGF-I levels and impaired measures of early atherosclerosis such as increased carotid intima-media thickness (Schut et al., 2003; Sesti et al., 2014). In epidemiological studies, low serum IGF-I was associated with increased risk of ischemic heart disease (Juul et al., 2002), congestive heart failure (Vasan et al., 2003), and increased CVD morbidity and mortality (Burgers et al., 2011; Carlzon et al., 2014; Svensson et al., 2012). However, little is known whether IGF-I is associated with vascular dementia (VaD). In rats with VaD, IGF-I and IGF-I mRNA were downregulated in the hippocampus (Gong et al., 2012), and deficiency of circulating IGF-I exacerbated hypertension-induced microvascular rarefaction in the mouse hippocampus and retrosplenial cortex (Tarantini et al., 2016). In human studies, serum IGF-I was reduced in VaD (Watanabe et al., 2005), and a polymorphism in the IGF-I receptor gene was more common in female VaD patients compared to female controls (Garcia et al., 2006).

The extent to which IGF-I is a risk factor for subsequent AD or VaD has previously not been studied in a memory clinic population. In this mono-center study of patients with subjective cognitive impairment (SCI) or mild cognitive impairment (MCI), we determined whether serum IGF-I concentrations were associated with the development of AD and/or VaD.

2. Materials and methods

2.1. Study participants

The Gothenburg MCI study is a longitudinal mono-center study performed at a memory clinic (Wallin et al., 2016a, 2016b). All included patients undergo baseline investigations to classify cognitive function and are then followed biannually (Wallin et al., 2016a, 2016b). Exclusion criteria included age < 40 or > 79 years, Mini Mental State Examination (MMSE) score < 19, acute/instable somatic disease, severe psychiatric disorder, substance abuse, or confusion caused by drugs. The included patients were classified using the global deterioration scale (GDS), in which GDS 4 equals possible mild dementia and GDS 1 equals no subjective or objective cognitive decline (Reisberg et al., 1988).

The recruitment of patients to the Gothenburg MCI study has previously been described in detail (Wallin et al., 2016b). Totally, 751 patients were included in the Gothenburg MCI study. Of these patients, 499 were classified as GDS 2 [equals subjective cognitive impairment (SCI)] or GDS 3 [equals mild cognitive impairment (MCI)]. One hundred and nine patients were excluded as they had no follow-up visit and 48 patients were excluded due to lack of adequate blood samples. Thus, all 342 patients classified with GDS 2 or 3 at baseline with at least one follow-up and stored blood samples for analysis of serum IGF-I were included in the present study.

The classification into GDS groups were based on medical history, checklists and instruments for cognitive symptoms as described previously (Wallin et al., 2016b): 1) Stepwise Comparative Status Analysis (STEP) (Wallin et al., 1996), variables 13–20 (memory disturbance, disorientation, reduced abstract thinking, visuospatial disturbance, poverty of language, sensory aphasia, visual agnosia, apraxia); 2) IFLEX, a short form of the Executive Interview (EXIT) (Royall et al., 1992); (number-letter task, word fluency, anomalous sentence repetition, interference task, Luria hand sequences, counting task); 3) MMSE (Folstein et al., 1975); and 4) Clinical Dementia Rating (CDR) (Morris, 1997). The CDR assessment was based on information from both the subject and an informant. The algorithm for GDS 2–3 was: STEP ≤ 1; I-FLEX ≤ 3; CDR ≤ 0.5; MMSE ≥ 26.

The follow-up time was calculated from the inclusion to the date of conversion to dementia (generally at one of the follow-up visits) or, for those who remained stable, to the last follow-up examination. The mean follow-up was 3.6 (SD 1.8) years. The maximum follow-up time was 6 years. During the follow-up, 95 patients converted to dementia. The clinician who determined the specific dementia diagnoses had access to magnetic resonance imaging (MRI) images but was blinded to neuropsychological test results and CSF biomarker data. AD was diagnosed according to the NINCDS-ADRDA criteria (McKhann et al., 1984).

VaD was defined as either the subcortical small vessel type of dementia (SSVD) according to the Erkinjuntti criteria (Erkinjuntti et al., 2000), or cortical vascular dementia (cVaD) using the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria (Román et al., 1993). More specifically: for SSVD, the patient had to have MRI-detected cerebral white matter changes (WMC) (mild, moderate, or severe according to Fazekas classification) (Wahlund et al., 2001) and predominant frontal lobe symptoms. If WMC were only mild, then SSVD was set only if parietotemporal lobe syndromes were not marked. A diagnosis of cVaD was set if dementia onset was stroke related (single- or multi-infarct). Of the totally 42 patients with VaD, 35 had SSVD, 6 had mixed forms of SSVD and cVaD, and one patient had cVaD.

Patients that developed mixed forms of AD and VaD ($n = 22$) were classified as VaD. More precisely, if AD patients also exhibited MRI findings of cerebral WMC (moderate or severe according to Fazekas classification) (Wahlund et al., 2001) with no predominant frontal lobe syndrome, or alternatively, mild degree of WMC in combination with a marked frontal lobe syndrome, these patients were defined as suffering from mixed dementia. As described previously (Eckerström et al., 2011; Nordlund et al., 2010), to have all patients with considerable vascular contribution to cognitive impairment in the same group, patients developing mixed dementia were included in the VaD group. Therefore, totally, 42 patients were diagnosed as suffering from VaD and 37 as AD.

Sixteen patients developed dementias other than AD or VaD. Lewy body dementia ($n = 2$), frontotemporal dementia ($n = 2$), and primary progressive aphasia (PPA; $n = 1$) were diagnosed as described previously (Wallin et al., 2016a, 2016b). Eleven patients converted to unspecified dementia.

2.2. Ethical considerations

The study was approved by the ethical committee at University of Gothenburg. Oral and written informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki.

2.3. Assessment of covariates

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Smoking habits as well as the presence of diabetes mellitus or hypertension was evaluated at the inclusion visit by a specialist physician.

2.4. Biochemical methods

Blood samples were drawn in the fasted state between 8 a.m. and 10 a.m. and then stored at -80 °C until the analysis of serum IGF-I concentrations, which were performed at one occasion 2015. The serum concentrations of IGF-I were determined using a chemiluminescent immunometric assay (IDS-iSYS; Immunodiagnostic Systems Limited, Boldon, United Kingdom) on an IDS-iSYS automated system (IS31040; Immunodiagnostic Systems Limited). The IDS-iSYS IGF-1 assay has been calibrated against the WHO International Standard 02/254.

Low-density lipoprotein (LDL)-cholesterol was calculated according to Friedewald's formula (Friedewald et al., 1972) based on routine clinical measurements of total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides.