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Hippocampal T2 hyperintensities on 7 Tesla MRI

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ABSTRACT

Hippocampal focal T2 hyperintensities (HT2Hs), also referred to as hippocampal sulcal cavities, are a common finding on Magnetic Resonance (MR) images. There is uncertainty about their etiology and clinical significance. In this study we aimed to describe these HT2Hs in more detail using high resolution 7 Tesla MR imaging, addressing 1) the MR signal characteristics of HT2Hs, 2) their occurrence frequency, 3) their location within the hippocampus, and 4) their relation with age. We also performed an explorative post-mortem study to examine the histology of HT2Hs.

Fifty-eight persons without a history of invalidating neurological or psychiatric disease (mean age 64 ± 8 years; range 43–78 years), recruited through their general practitioners, were included in this study. They all underwent 7 Tesla MRI, including a T1, T2, and FLAIR image. MR signal characteristics of the HT2Hs were assessed on these images by two raters. Also, the location and number of the HT2Hs were assessed. In addition, four formalin-fixed brain slices from two subjects were scanned overnight. HT2Hs identified in these slices were subjected to histopathological analysis.

HT2Hs were present in 97% of the subjects (median number per person 10; range 0–20). All HT2Hs detected on the T2 sequence were hypointense on T1 weighted images. Of all HT2Hs, 94% was hypointense and 6% hyperintense on FLAIR. FLAIR hypointense HT2Hs were all located in the vestigial sulcus of the hippocampus, FLAIR hyperintense HT2Hs in the hippocampal sulcus or the gray matter. Post-mortem MRI and histopathological analysis suggested that the hypointense HT2Hs on FLAIR were cavities filled with cerebrospinal fluid. A hyperintense HT2H on FLAIR proved to be a microinfarct upon microscopy.

In conclusion, hippocampal T2Hs are extremely common and unrelated to age. They can be divided into two types (hypo- and hyperintense on FLAIR), probably with different etiology.

1. Introduction

On MR images of the hippocampus, focal T2 hyperintensities, also referred to as hippocampal sulcal cavities, are a common finding. They are reported to be hypointense on T1 and hyperintense on T2 weighted images. Most studies hypothesized that these T2 hyperintensities are anatomic variations, thought to occur during development as a result of incomplete folding of the hippocampus, leading to small fluid collections – i.e. cavities – in the vestigial sulcus of the hippocampus [1,2]. Others, however, argue that the T2 hyperintensities are lesions related to ischemic or hypoxic events [3,4]. This ambiguity concerning their origin is also reflected in the various names they received including hippocampal sulcal cavities, low signal foci, and hyperintense lesions. In our view it is best to name them according to their MR features, without prior assumptions on their etiology. In the present paper we will therefore refer to them as focal hippocampal T2 hyperintensities, abbreviated as HT2Hs.

A recent review of the MR literature reported that HT2Hs are very common with a mean prevalence of 47% in healthy older controls, though reported numbers vary considerably [5]. Also, the relation of HT2Hs with age [1,6,7], vascular risk factors [5], or memory [4,2,8] is not clear. Until now, HT2Hs have mostly been investigated using T1 or T2 weighted images that cannot differentiate between fluid-filled hippocampal cavities and gliotic ischemic lesions. Furthermore, they have solely been described on conventional field strength MRI, often

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using thick slices (5 mm or more), which might have led to an underestimation of their occurrence.

In this study we describe HT2Hs at 7 Tesla MRI using T1, T2, and fluid-attenuated inversion recovery (FLAIR) images in people without known neurological disease. We aimed to describe 1) the MR signal characteristics of HT2Hs on T1 and FLAIR, 2) their occurrence, 3) their location within the hippocampus, and 4) their relation with age, blood pressure, cognition, and other brain MRI markers. Finally we performed an explorative post-mortem study in brain material from other subjects to examine the histology of these HT2Hs.

2. Material and methods

2.1. Study population

Subjects were recruited through their general practitioners as part of two related cohorts with similar experimental work-up (PREDICT-MR; a prospective cohort MR study of individuals attending their general practitioner, not selected for presence of specific medical conditions [9] and UDES2; a study on MRI correlates of type 2 diabetes mellitus that included both participants with and without diabetes [10]). From these studies we selected all participants that met the following criteria: 1) age above 40, 2) no known psychiatric or neurological disorder that could affect cognitive functioning, 3) a Mini-Mental State Examination (MMSE) score of 25 or higher, 4) no contraindications for 7 Tesla MRI (e.g. metal in or on their bodies, claustrophobia), and 5) 7 Tesla T1, T2, and FLAIR. From the UDES2, all controls and a random sample of the patients with diabetes, in accordance with the prevalence of type 2 diabetes mellitus in the Dutch population (14%), were eligible for the present study. The total study sample comprised 58 subjects (Fig. 1).

PREDICT-MR and UDES2 were approved by the medical ethics committee of the University Medical Center Utrecht (UMCU), and all subjects gave written informed consent.

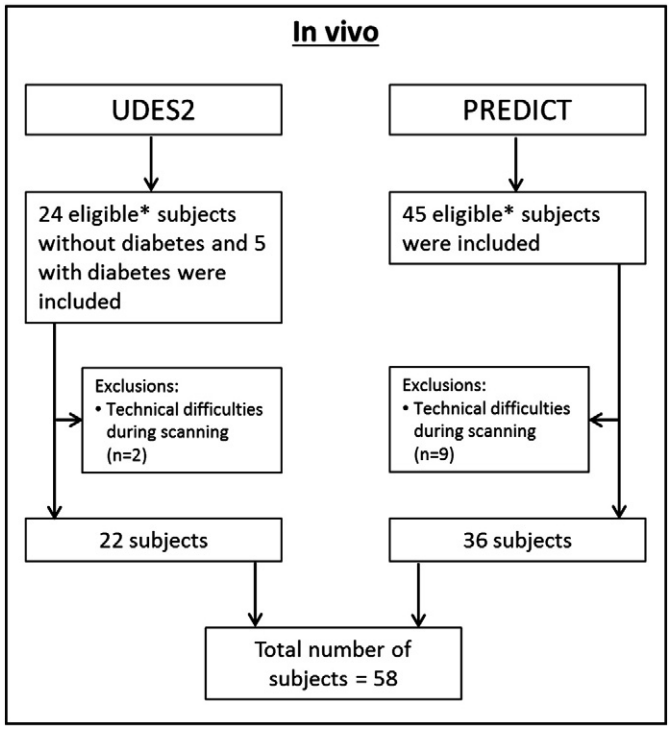

Fig. 1. Flowchart of study participants. *Subjects were eligible for the current study when they met the following criteria: 1) age above 40, 2) no known psychiatric or neurological disorder that could affect cognitive functioning, 3) a Mini-Mental State Examination (MMSE) score of 25 or higher, 4) no contraindications for 7 Tesla MRI (e.g. metal in or on their bodies, claustrophobia, and 5) T1, T2, and FLAIR.

All participants underwent a standardized evaluation, including medical history, physical (e.g. blood pressure), neurological, and neuropsychological examination. On the same day all participants underwent conventional (PREDICT-MR 1.5 T; UDES2 3 T) and 7 Tesla MRI. With respect to the neuropsychological examination, in this study we primarily focused on memory. A composite z-score for memory was calculated based on the immediate, delayed recall and the retention score of the 15-word learning test (a modification of the Rey Auditory Verbal Learning test). Composite z-scores were computed by converting raw scores to standardized z-scores and averaging them across all subtests.

2.2. MRI scanning protocol

Scans were acquired on a whole-body 7 Tesla MR system (Philips Healthcare, Cleveland, OH, USA) with a volume transmit and 16-channel receive head coil (Nova Medical, Wilmington, MA, USA). Subjects included in the study later than May 2011 were scanned with a volume transmit and 32-channel receive head coil (Nova Medical). The standardized protocol included the following sequences:

- Volumetric (3D) magnetization prepared (MP-) FLAIR with an acquired, isotropic resolution of $0.8 \times 0.8 \times 0.8$ mm^3, repetition time (TR) = 8000 ms, nominal echo time (TE) = 300 ms using constant low refocusing angles of 70°, inversion time (TI) = 2325 ms, matrix size = 312×304. Scan duration 12 min 48 s.
- 3D T2 weighted turbo-spin echo (TSE) with an acquired, isotropic resolution of $0.7 \times 0.7 \times 0.7$ mm^3, TR = 3158 ms, nominal TE = 346 ms with a variable refocusing flip angle sweep, leading to an equivalent TE (for T2 contrast) of approximately 57 ms for gray and white matter, matrix size = 356×357. Scan duration 10 min 15 s.
- 3D T1 weighted sequence with an isotropic resolution of $1.0 \times 1.0 \times 1.0$ mm^3, flip angle 8°, TR = 4.8 ms, TE = 2.2 ms, TI = 1240 ms, TR of the inversion pulses = 3500 ms, matrix size = 200×250. Scan duration 1 min 57 s.

2.3. Visual rating and volume assessment

Two raters (SvV and LW), blinded to subject information, independently assessed MR signal characteristics, number, and location of the HT2Hs on T2, T1, and FLAIR 7 Tesla images. In case of disagreement a consensus meeting was held and if necessary discussed with a neuroradiologist (JH).

One rater (LW) assessed total hippocampal volume and volume of HT2Hs on consecutive slices of the T2 weighted 7 Tesla images using an in-house developed software program (by HK), based on MeVisLab (MeVis Medical Solutions AG, Bremen, Germany [11]) [9]. The volume of HT2Hs was assessed again after a four-week interval in a randomly chosen sample of 15 subjects to establish intra-rater reliability. The intraclass correlation coefficient for total hippocampal volume was 0.98 [9].

White matter hyperintensities (WMHs) and lacunar infarcts were assessed on 3 Tesla 2D FLAIR (voxel size $1.0 \times 1.3 \times 3.0$ mm^3) and 3D T1 (voxel size $1.0 \times 1.0 \times 1.0$ mm^3) (UDES2) or 1.5 Tesla 3D FLAIR and 3D T1 (PREDICT-MR; both with voxel size $1.1 \times 1.1 \times 1.1$ mm^3) using the age-related white matter changes (ARWMC) scale [12]. We choose not to use the 7 Tesla scans for these ratings, because the ARWMC scale has not yet been applied to scans of this field strength. Two independent raters rated WMHs and lacunar infarcts. In case of disagreement a consensus meeting was held.

2.4. Post-mortem study

Post-mortem brain tissue of two patients, who were autopsied in the UMCU, was scanned in an overnight scanning session as part of another study [13]. They were included as an explorative post-mortem study to examine the nature of the observed in vivo HT2Hs with histology.