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Imaging brain amyloid in nondemented young adults with Down syndrome using Pittsburgh compound B

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Abstract Down syndrome (DS) is one of the most common causes of intellectual disability. Although DS accounts for only 15% of all individuals with intellectual disabilities, adults with DS account for approximately 60% of individuals with intellectual disabilities and Alzheimer's disease. This is thought to be because of overproduction of the β-amyloid (Aβ) protein due to trisomy for the Aβ precursor protein gene on chromosome 21. Pittsburgh compound B (PiB) is a noninvasive in vivo positron emission tomography tracer used to image amyloid deposition in living humans. Studies using PiB have shown an age-dependent asymptomatic amyloid deposition in more than 20% of the cognitively normal elderly population. Presymptomatic carriers of presenilin (PS-1) and Aβ precursor protein gene mutations who are destined to develop Alzheimer's disease also show preclinical amyloid deposition. This report describes a pilot study involving the use of PiB in seven adults with DS (age: 20–44 years). Compared with objective cutoffs for amyloid positivity in older non-DS cognitively normal control subjects, only two of the seven DS subjects (age: 38 and 44 years) showed increased PiB retention. The remaining five subjects aged between 20 and 35 years showed no detectable increase in PiB retention. Interestingly, the two subjects who showed elevated PiB retention showed a striatal-predominant pattern similar to that previously reported for PS-1 mutation carriers. These results demonstrate the feasibility of conducting PiB positron emission tomography scanning in this special population, and suggest a link between Aβ overproduction and early striatal deposition of fibrillar Aβ.

Keywords: Down syndrome; Intellectual disability; Alzheimer's disease; Pittsburgh compound B; Amyloid deposition

1. Introduction

Down syndrome (DS) is one of the most common causes of intellectual disability, accounting for approximately 15% of all individuals with intellectual disabilities. The incidence of DS is 1:800 live births, with an estimated 7000 babies born with DS annually [1]. Although the incidence of Alzheimer's disease (AD) among individuals with intellectual disabilities has been found to be no different than among those in the neurotypical population [2], adults with DS comprise up to 60% of individuals with intellectual disabilities who show signs of AD [3,4]. Evidence suggests that individuals with DS experience premature aging, perhaps as much as 20 years earlier than would be expected in normal aging. It is also known that individuals with DS develop AD at an early age and progress rapidly [5].

Although the average life expectancy of individuals with DS remains lower than that of neurotypical adults, the number of older DS adults has been increasing. The current mean life expectancy exceeds 50 years, with 20% or more of the DS population now aged >55 years [6,7]. The fact that more than a third of DS adults aged >50 years and more

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than one half of DS adults aged >60 years have been diagnosed with AD presents a significant public health problem [8]. Additionally, it has been recently demonstrated that DS subjects aged >45 years show significant cortical Pittsburgh compound B (PiB) uptake, regardless of dementia diagnosis [9]. It is important to note that age-associated decline among nondemented individuals with DS through the fifth and even sixth decade of life is not inevitable, although is does occur in many individuals [10]. Consequently, changes in cognitive functioning in this population are likely to be indicative of early stages of AD, after other potential causal factors, such as hypothyroidism or depression, are ruled out.

Postmortem studies of brain tissue in individuals with DS have shown neuropathological changes similar to those observed in individuals diagnosed with AD, characterized by the presence of neurofibrillary tangles and neuritic plaques in the brains of almost all DS individuals by 40 years of age [11,12]. In one study, the mean age at onset of dementia in patients with DS was 56 years, and prevalence increased from 11% between the ages of 40 and 49 years to 77% between the ages of 60 and 69 years. All subjects aged ≥70 years had dementia [5]. In contrast, the prevalence of dementia in the non-DS population from all causes among those aged ≤65 years was found to be <5% and it increased to 13% for those aged >65 years [13]. It is believed that this high incidence of dementia in the DS population is due to the extra copy of chromosome 21, which codes for the β-amyloid (Aβ) precursor protein (APP) gene. Studies by Hyman and colleagues have shown that the level of amyloid deposition in the brains of individuals with DS is higher than in individuals with AD [11,14]. This may be particularly true in individuals with the trisomy 21 variant, the most common cause of DS.

Definitive diagnosis of AD relies on the demonstration of amyloid plaques and neurofibrillary tangles at autopsy [15,16]. The time course of amyloid deposition in AD has not been definitively elucidated, but evidence gained through postmortem studies of individuals with DS suggests that amyloid deposition begins over a decade before the clinical symptoms of dementia. Studies in carriers of PS-1 mutations have shown clear evidence that Aβ deposition predates dementia by at least 10 years [17]. Unexpectedly, PiB retention in some presymptomatic PS-1 mutation carriers appears to begin in the striatum [17], an area affected later in the course of late-onset AD [18].

This report describes a pilot study using PiB positron emission tomography (PET) in nondemented DS subjects. The objectives of this study were threefold. First, we sought to demonstrate the feasibility of conducting PiB PET studies in this special population. Second, we sought to assess the pathophysiological process of fibrillar Aβ deposition in the brains of DS subjects of increasing age. Finally, PET data from these subjects were compared with historical PiB PET data obtained from normal control subjects between the ages of 35 and 80 years.

2. Methods

2.1. Participant characterization

Subjects were recruited over a 22-month period from our university's adult DS center and psychiatric clinic for adults with developmental disabilities. In addition, letters were sent out to families with DS patients in western Pennsylvania (using the DS center's database). Interested families were contacted by telephone and underwent a thorough screening to determine study eligibility (i.e., subjects with a history of claustrophobia, with metal in their bodies, or with a current AD diagnosis were excluded). As a result, all subjects who were invited to participate in the study met study inclusion criteria. All subjects and their caregivers (when appropriate) provided informed consent for both clinical examination and the PET imaging protocol. This study was approved by the Human Use Subcommittee of the Radioactive Drug Research Committees and the Institutional Review Board of the University of Pittsburgh. Subjects had to be at least 20 years of age, have an intelligence quotient of ≥40, and have documented evidence of trisomy 21. Subjects could have no evidence of significant cognitive decline over the previous 1 year using a "Stability/Decline Scale" designed specifically for this study (see later in the text). Other exclusion criteria included any significant disease or unstable medical condition that could affect neuropsychological testing and conditions for which magnetic resonance imaging (MRI) was contraindicated.

2.2. Initial screening

Participants initially provided consent and were subsequently assessed to obtain baseline measures of cognitive and adaptive functioning using the measures mentioned in the following text.

2.2.1. Stanford–Binet Abbreviated Battery IQ

All subjects were given the Stanford–Binet Abbreviated Battery IQ [19] to obtain an updated estimate of cognitive functioning. The Stanford–Binet Abbreviated Battery IQ includes both a verbal and nonverbal subscale and produces an abbreviated intelligence quotient score (mean: 100; SD: 15) as well as a mental age.

2.2.2. Severe Impairment Battery

The Severe Impairment Battery [20] is composed of 40 simple one-step command items that are scored on a 3-point scale. Overall, scores can range from 0 to 100, with lower scores indicating greater levels of impairment.

2.2.3. Stability/Decline Scale for DS

The Stability/Decline Scale for DS was developed specifically for the current study. Caregivers who had consistent and substantial (≥4 days/week) contact with the subject for at least 1 year were asked to rate the subject's functioning in areas of language, understanding, memory, self-care, and