Journal of Alzheimer's
Disease Reports
Volume 9: 1–7

DOI: 10.1177/25424823241298530
journals.sagepub.com/home/alr

A historic case of relapsing-remitting Alzheimer's disease in an adolescent attributed to scarlet fever

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Abstract

We draw attention to a historic case of a boy who suffered from scarlet fever (typically caused by the bacterium *Streptococcus pyogenes*) at age 7 years and went on to develop the symptoms of Alzheimer's disease (AD). His physicians believed that the subsequent dementia was related to the infection. After death at 24 years of age, postmortem brain examination revealed abundant AD-type senile plaques and fibrils, formally confirming AD. Other potential causes of early-onset dementia are discussed, but these are distinct from patient E.H. This case is pertinent regarding the current debate about the potential role of infection in AD.

Keywords

adolescent, Alzheimer's disease, early onset, historic, infection, relapsing-remitting, *Streptococcus*

Received: 3 September 2024; accepted: 21 October 2024

An unusual case from 100 years ago might inform more widely on the potential causes of dementia. Although Alzheimer's disease (AD) is generally recognized as a disease of the elderly, much younger individuals are sometimes affected. McMenemey cited individuals with onset in their 30 s to 50 s.[1] One of the most intriguing cases, however, is that of a patient who at the beginning of the past century had onset of mental deterioration and frank dementia, with confirmed Alzheimer pathology, all under the age of 24 years.

As described in detail by Malamud and Lowenberg, physicians at the Foxburgh Hospital in Massachusetts, USA, a young boy, E.H., born in 1902 (presumed to be from the same region), went on to develop what appears to be classic AD in adolescence.[2] In his earliest years his parents attested that he was bright and mentally normal. At age 7 he had an attack of scarlet fever, a disease predominantly caused by *Streptococcus pyogenes*. Following scarlet fever, he entered a decline, made no progress at school for several years, and at age 15 he was admitted to a state school for feebleminded children and subsequently to a hospital for the insane.

Examination at admission confirmed that his memory was poor, he had little grasp of his surroundings, and uncovered signs of an old tuberculous process. At this time, he had an attack of infectious arthritis, a disease caused by bacterial, fungal, or viral infection of the joints (the most common infection is with *Staphylococcus*, but *Streptococcus* is also a known contributor).

This then cleared up, and at age 16 he was up and about, helping with ward work, and had some grasp of his surroundings. This recovery did not continue, and by 1920 at age 18 he was becoming progressively worse mentally.

Nevertheless, he again showed recovery. He was discharged from the hospital and, now 21 years old, Malamud and Lowenberg wrote 'In January, 1923, it was reported that he was getting along well and was helping a neighbor on a milk route'.

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Box 1. Childhood dementias and other conditions

'Early-onset' or 'young-onset' AD is not unknown, but typically results from genetic mutations such as in *APP*, *PSEN1*, or *PSEN2*, with onset in the 40–60 age group.[4] Indeed, 'young onset' is misleading in this context because the term has been used to describe any case under 65 years of age.[5] AD onset in the 30 s has been reported,[6,7] but such cases are very unusual.

One potential parallel to the present case is that of a 19-year-old adolescent with suspected AD,[8] but the picture was mixed and was possibly consistent with hippocampal damage, as in the famous surgical patient H.M.,[9] rather than with AD. His short-term memory was acutely affected, and he could not remember whether he had eaten or not (as H.M.), but there were no obvious personality changes, and he was able to live independently, suggesting that long-term memory was intact (as in H.M.). Moreover, amyloid and tau tracer imaging revealed no abnormal deposits in brain. There was mild atrophy of the hippocampus, but this was restricted to the formation. No pathological mutations were detected. The $A\beta_{42/40}$ ratio in CSF (0.06 increasing to 0.08) was borderline to normal. By contrast, p-Tau (Innotest pTau181) subject values were 52 and 80, to be compared against control 33–39 (means of three independent cohorts) versus 72–117 in confirmed AD using the same test.[10] However, there was no evidence of an infectious component, at least for HIV and syphilis.

True dementias of childhood, that have mean age of onset of 2.5 years, are generally associated with damaging genetic mutations (e.g., lysosomal and mitochondrial disorders), show a range of serious comorbidities and a steady course of progression, and have a median survival of ~9 years;[11] this may be an unlikely scenario in the present case. Wisniewski et al. reported on seven young patients with diagnoses ranging from subacute sclerosing panencephalitis (SSPE) to lead encephalopathy, tuberous sclerosis, Hallevarden–Spatz disease (now known as Pantothenate kinase-associated neurodegeneration, PKAN; two cases), pigment-variant lipofuscinosis, and Down syndrome (DS), all with mental retardation and/or other neurological deficits.[12] Mean age of onset was 3.5 years (range 1–8), with median survival of 13 years (range 8–27). Postmortem examination revealed neurofibrillary tangles, demonstrating that these are not exclusive to AD. However, these cases differed from E.H. in two important respects. **First,** with the exception of the sole patient with DS, none showed Aβ senile plaques, and even in the DS patient plaque density was very low. **Second,** all showed a constant trajectory of deterioration, whereas E.H. presented a relapsing-remitting course of disease. SSPE is notable in this context because the disease, that is now generally attributed to early infection with wild-type measles virus, can sometimes show periods of remission followed by relapse,[13] but such cases are negative for Aβ.[14]

Frontotemporal dementia (FTD), that is commonly associated with *GRN*, *MAPT*, or *C9ORF72* genetic mutations, can have very early onset, and cases have been reported with onset at 14,[15] 17,[16] and 30 years of age.[17] However, FTD cases are typically Aβ-negative, in contrast to E.H., although some individuals in the older age-brackets can present evidence of dual FTD and AD pathology.[18]

Another neurodegenerative condition, Parkinson's disease, can have onset as early as 25 years (young-onset PD) or 17 years (juvenile PD), but these are generally Aβ-negative, have a later onset, and dementia is generally entirely absent from these early-onset cases.[19,20]

There are also similarities to pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) and its relative, pediatric acute-onset neuropsychiatric syndrome (PANS). Swedo et al. reported on a first series of 50 cases of PANDAS following primary infection with *Streptoccus* spp. including *S. pyogenes*.[21] Symptom onset was typically at around 6 years of age (range 2–12 years) following the initial fever. These cases are reminiscent of E.H. because a relapsing-remitting profile is often present (as in multiple sclerosis). However, there are major discordances. First, the symptoms of PANDAS are predominantly of obsessive/compulsive disorder (OCD) and/or tics associated with basal ganglia involvement, as well as with attentional problems suggestive of attention-deficit hyperactivity disorder (ADHD), but psychosis and dementia are absent. Similar observations have been made in PANS.[22] Second, there is no evidence for amyloid deposits in these cases, although this could be because few have come to postmortem examination. An exception is the tragic suicide of a young woman with PANDAS, OCD symptoms, and severe anxiety;[23] postmortem examination revealed Alzheimer's type II astrocytes, but there was no microgliosis or overt amyloid deposits, her overall cognitive skills were normal, and there were no indications of dementia.

Lyme disease, caused by *Borrelia burgdorferi*, may result in neuroborreliosis which is known to be associated with dementia.[24–27] However, dementia is very rare complication of Lyme disease, and the few

cases encountered are typically in the elderly; the mean age in the study of Blanc et al. was 67 years (range 43–79). Lyme disease in children and adolescents does occur but the symptoms are restricted to flu-like symptoms; neuropathy and CNS involvement were not found in this age group.[28]

Neurosyphilis is another potential contender. The causal agent, *Treponema pallidum*, is primarily transmitted through sexual contact, and disease is thought to take many years to progress. Brain involvement (neurosyphilis) generally has an onset at around 40 years of age[29] and can present with dementia resembling AD.[30] Cases in their 30 s have been reported.[31–33] One exceptional case was reported of a 15-year-old girl and rape victim with neurosyphilis who presented with marked psychotic features and Parkinsonism;[34] however, the circumstances of E.H. are not suggestive of acquired syphilis infection in childhood. However, the agent can be passed to offspring in pregnancy, where it is associated with both prenatal and postnatal abnormalities, but brain involvement is less common.[35] Nevertheless, one 17-year-old woman showed progressive cognitive decline since the age of 8 and was diagnosed with late-onset congenital syphilis.[36]

The presence of tuberculous lesions is suggestive because active tuberculosis in the elderly can be associated with dementia,[37,38] and tuberculous meningitis in childhood can lead to cognitive impairments.[39] However, childhood dementia has not been reported in tuberculosis.

Herpes viruses can lead to encephalitis in childhood, the principal symptoms of which are fever and confusion, often with seizures,[40,41] but dementia in childhood with this infection has not been reported.

We therefore return to *Streptococcus pyogenes* that is a known cause of childhood meningitis[42–44] as well as of PANDAS/PANS, and that has previously been associated with invasive central nervous system infection and dementia in adulthood.[45] However, progression to dementia in childhood has not previously been reported to our knowledge.

At the beginning of 1926 (23 years of age) there was another turn for the worse. 'He had a cold about that time, and, although physically not very ill, began to show signs of mental disturbance', and he returned to the hospital. He then developed a fever (temperature 102.6°F, 39.2°C) and a lung infection, his physical condition became worse, and he died in October 1926 at just short of 24 years of age. The specific cause of death is unknown. Postmortem examination found caseous abscesses (necrosis with tissue softening) in his lungs that were ascribed to an acute tuberculous process.

Brain rarefaction and marked degenerative changes were recorded: 'The most prominent type was that of the Alzheimer fibril change: it was represented without exception in all areas of the brain … Numerous senile plaques were found throughout all parts of the cortex' with 'highest intensity in Ammon's horn' (i.e., hippocampus), as is often the case in typical AD. There was a potential link to cerebral vasculature: 'In the occipital lobe, some of the capillaries were surrounded by rings of necrotic tissue … in other places some of the vessels were surrounded by plaques'. In short, this was 'an extremely advanced, typical picture of Alzheimer's disease' (Figure 1).

In discussion of the case Malamud and Lowenberg state 'There is not a doubt that the definite change at the age of 7 was in some way or other related to it' {scarlet fever}. However, they specifically drew attention to remission: 'after the establishment of the typical clinical picture with definite progression, there was a remission (more or less complete) that lasted about four years'.

Although their account highlights a period of remission lasting 3–4 years, it suggests at least two periods of recovery for 2–4 years followed by clinical decline. This pattern of remission and relapse is reminiscent of another brain disorder, relapsing-remitting multiple sclerosis (MS), where relapses tend to occur every few years (which is also a feature of some other childhood disorders such as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection, PANDAS; Box 1). MS has a strong immune/inflammatory component[46] and has been linked to infectious agents such as Epstein–Barr virus.[47] Interestingly, genes predisposing to MS (as with AD) predominantly involve the immune system.[48] However, the ϵ4 allele of *APOE*, a key risk factor for AD and for some infectious diseases, does not show a clear association with MS,[49] pointing to an independent pathoetiology. In addition, although dementia similar to that of AD may be often overlooked in MS patients,[50] there are distinct differences in the neuropathology of MS as compared to AD.[51]

A key particularity of case E.H. was intense postmortem pathology of the choroid plexus—the brain tissue that produces cerebrospinal fluid and that constitutes the barrier between the blood and cerebrospinal fluid.[52] MS has also been associated with involvement of the choroid plexus.[53,54] In debating the possible multiplicity of causal factors in E.H., Malamud and Lowenberg state: 'The possibility of a disturbance of the plexus … would offer a stepping stone towards discovering such a causal factor.' This is undoubtedly insightful given that the choroid plexus in particular may play a pivotal role in modulating different types of neurological infections,[55] including severe COVID-19.[56] With regards to COVID-19 infections, memory and related problems have been reported in children following infection.[57] There is also evidence in young adult COVID patients of brain amyloid, but not necessarily due to infection.[58] Looking wider, it is possible

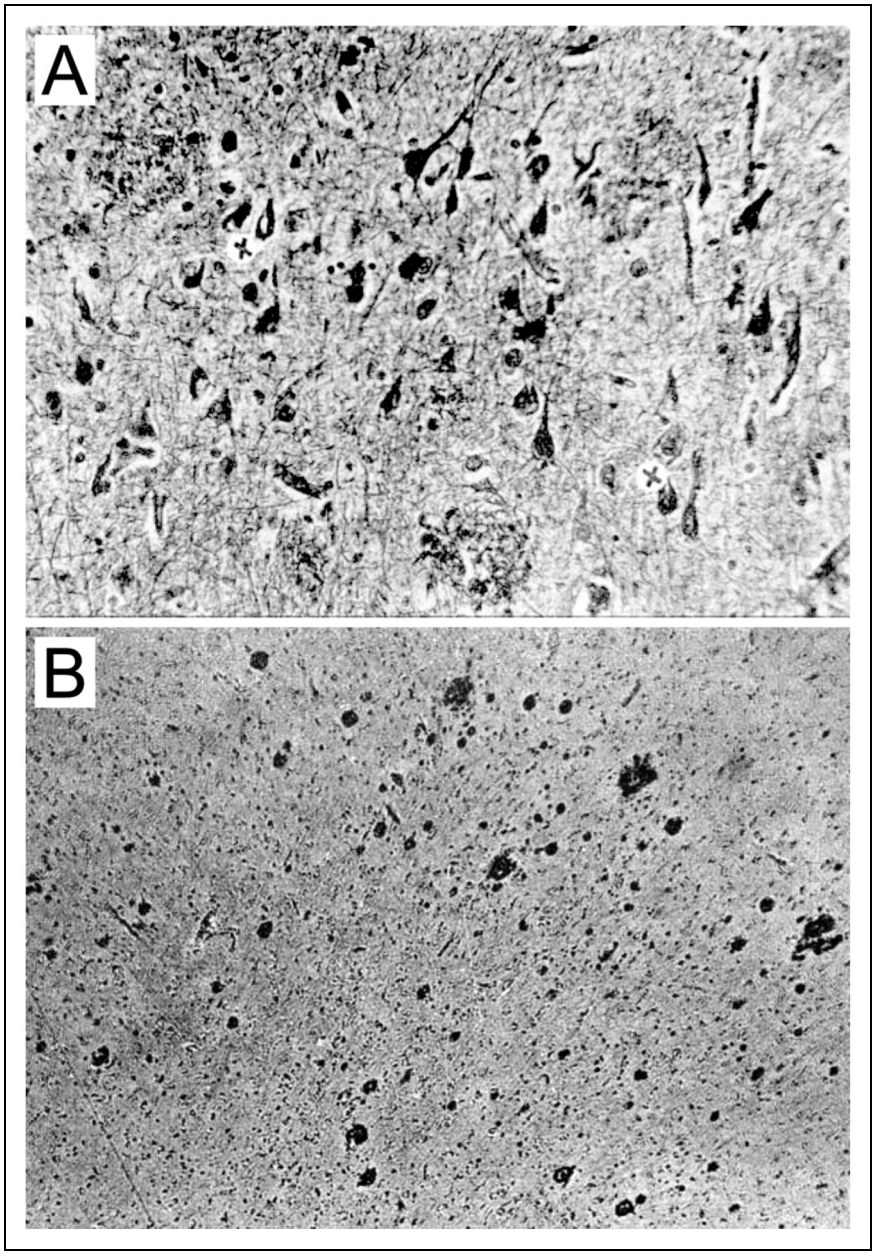

Figure 1. Alzheimer pathology in case E.H. (A) Fibrillar changes (×200) and (B) senile plaques (×40) in cortex. Panels reproduced, with permission, from Malamud and Lowenberg.[2] The silver-based methods employed primarily stain neurofibrillary tangles and senile plaques.[3] In E.H. the most prominent pathology was of Alzheimer fibrils that were found in all areas of the brain, with highest intensity in hippocampus. Senile plaques were particularly numerous in hippocampus and of an unusually large size and were seen in other areas of temporal lobe. The vessels of the choroid plexus were also strongly affected, with greatly thickened walls around the lumen that in most cases occluded the lumen entirely. No pathology was observed in cerebellum (not shown).

that the population burden of COVID-19 could contribute to escalating rates of AD, perhaps affecting younger individuals.[59]

The cause of adolescent-onset dementia in this case remains unknown, but an association with the primary infectious condition was presumed to be central. AD has not so far been causally linked to *Streptococcus pyogenes*, but such cases may have gone unreported. The family noted no unusual pattern of illnesses in infancy, arguing against an underlying immunodeficiency condition, although this cannot be ruled out, and the attack of infectious arthritis (at age 15) and the presence of tubercular lesions should be borne in mind. In this regard, a combination of different pathogens (polymicrobial insult) might act synergistically leading to neuronal damage and overall symptomatology.

As discussed in Box 1, none of several other potential causes provide a satisfactory explanation, notably because other cases of young-onset dementia are generally negative for AD-type amyloid (although AD-like fibrillar neuropathologies may be present), and the case of E.H. is therefore exceptional in which both senile plaques and neurofibrillary tangles were identified (Figure 1). There are cases of AD without demonstrable Aβ amyloid senile plaques,[60] as well as numerous clinical cases of asymptomatic individuals where amyloid plaques are widespread.[61] Thus, there is no one-to-one association between amyloid and disease. For the present case, the closest parallel is perhaps with PANDAS that can be linked to *S. pyogenes* infection, but the single case that came to postmortem examination found no evidence of Aβ senile plaques (discussed in Box 1) and obsessive-compulsive behaviors (a characteristic feature of PANDAS) were absent in E.H, arguing against a diagnosis of PANDAS. At face value, it would appear to be a case where relapsing-remitting dementia of the Alzheimer's type was triggered following infection with *S. pyogenes* or a related organism, which fits with the emerging concept that Aβ is an antimicrobial peptide that defends against brain infection,[62–64] leading to the antimicrobial protection hypothesis of AD.[65] One presumes that clinical samples from this specific patient were lost years ago, but clinicians are encouraged to be alert to similar conditions because molecular analysis would inform on the primary etiology. Nevertheless, no other case of progression of *S. pyogenes* infection to AD in adolescence has been reported, and what sets this case apart is entirely unknown. We highlight this intriguing case because of increasing interest that AD might be precipitated by infection and of cases where appropriate antimicrobial intervention has been associated with remission.[66]

Acknowledgments

The authors have no acknowledgments to report.

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Statements and declarations

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Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

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