Original Article

Gaining Insights into Alzheimer's Disease through Pedigree Analysis in a Bangladeshi Context

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ABSTRACT:

Introduction: *Alzheimer's disease (AD) is a prevalent and irreversible neurodegenerative condition, ranking as the seventh leading cause of global mortality. This complex ailment encompasses various clinical and imaging-based classifications. Nonetheless, the use of pedigree analysis offers an additional layer of insight by delineating inheritance patterns, thus categorizing AD into familial and sporadic types. This study sought to determine the prevalence and characterization of different AD types through pedigree analysis, while also examining the age at which the disease manifests.*

Methods: *Conducted within the Department of Anatomy at BMU, this cross-sectional descriptive investigation encompassed thirty-seven patients, selected through rigorous sample size calculations and meeting specific inclusion and exclusion criteria under the oversight of a registered Neurologist from the Department of Neurology at BMU. Pedigrees were meticulously constructed following international pedigree drawing guidelines, employing the Genetic pedigree chart creation software, f-tree (version 4.1.0).*

Results: *Among the 37 clinically diagnosed AD patients, 27% (10) exhibited familial AD, while the remaining 73% (27) presented as sporadic AD cases. Within the familial AD group, 70% (7) suffered from Early-Onset Alzheimer's Disease (EOAD), and 30% (3) had Late-Onset Alzheimer's Disease (LOAD). Conversely, of the sporadic AD cases, 14.81% (4) were EOAD, while the vast majority, 85.19% (23), were LOAD.*

Conclusions: *This research demonstrates that pedigree analysis offers valuable insights into the classification of AD types, improving genetic counseling, enabling early diagnosis, enhancing disease management, and prognosis. These findings could ultimately alleviate the burden on affected families and the healthcare system as a whole.*

Key Words: Alzheimer's disease, familial AD, sporadic AD, early onset AD, late onset AD, pedigree

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Introduction

Alzheimer's Disease (AD) is a prevailing irreversible brain degenerative condition imposing a substantial economic burden on affected individuals, caregivers, and society[1] while ranking as the seventh leading cause of death globally.[2]

Once investigated Alzheimer's disease (AD) from a family history perspective, it can be categorized into familial AD and sporadic AD[3], additionally, from an age-related standpoint, AD can be divided into early onset AD (occurring before age 65) and late onset AD (occurring at age 65 or older).[4,5] Familial AD usually passes from parent to child in an autosomal dominant pattern and occurs exclusively at an early age[6] while sporadic AD occurs as an isolated case within a family and appears at late age.[7] Distinguishing between the different types of Alzheimer's disease can be achieved through pedigree analysis, a visual representation of a family's composition and medical history. Constructing a pedigree involves a systematic approach using standardized symbols and conventions.[8] Pedigrees are valuable tools for pinpointing individuals and families at higher risk of genetic issues, thereby facilitating enhanced genetic counseling, screening, and diagnostic testing to promote disease prevention, early diagnosis, and effective management.[9]

To the best of the researcher's knowledge, no studies of this kind have been conducted in the context of Bangladesh. Given this gap, if various types of AD can be precisely diagnosed through pedigree analysis, this study was aimed to ascertain the types and frequencies of different AD variants within the adult Bangladeshi AD patient population using pedigree analysis. Thus, it could significantly contribute to early detection, improved management, and the prevention of the disease through genetic counseling. Furthermore, it could assist in future planning, including financial, family, and caregiver planning, thereby reducing the burden on both affected families and the nation as a whole.

This study was aimed to ascertain the types and frequencies of different AD variants within the adult Bangladeshi AD patient population using pedigree analysis.

Materials and Methods

The present research was designed as a cross-sectional descriptive study and was conducted in the Department of Anatomy at Bangladesh Medical University (BMU), Dhaka, Bangladesh, from September 2022 to August 2023, following formal approval from the Institutional Review Board (IRB) of BMU. Diagnosed AD patients were selected from the Neurology Department and Dementia Clinic of BMU. Based on the sample size calculation, thirty-seven patients were chosen using specific "selection checklist" and confirmed by a registered neurologist, following specific inclusion and exclusion criteria. For patient selection, the Mini-Mental State Examination (MMSE) score was utilized. A cut-off score of <24 on the MMSE, indicating cognitive impairment[10], was used to identify patients with Alzheimer's Disease. In this study, all participants had MMSE scores in the range of 21-23. The inclusion criteria were defined as patients aged 30 years and above, in line with recent reports from Johns Hopkins Medicine and Harrison's Principles of Internal Medicine, which state that AD can manifest as early as the third decade of life.[11,12] Participants of any gender and Bangladeshi nationality were included. Exclusion criteria comprised conditions that could mimic AD, such as cerebral infections, Down syndrome, history of recurrent stroke, and Parkinson's disease. Informed consent was obtained from each patient, and personal and family histories were collected using a structured data collection sheet. Of the 37 participants in the study, 11 were aged 30 to 65, representing early-onset Alzheimer's Disease (EOAD) cases, while 26 were aged 65 and above, representing late-onset Alzheimer's Disease (LOAD) cases. The 37 participants were belong to 35 distinct families.

A detailed history was meticulously taken regarding maternal and paternal families for three to five generations using a data collection sheet. Here, only clinical data were taken. The collected information was entered into the genetic pedigree chart creation software f-tree version 4.1.0, which automatically generated the pedigrees. In this research, patients with a positive family history of AD (at least one affected relative in any generation) were classified as having familial Alzheimer's Disease, while others were classified as having sporadic Alzheimer's Disease. Subsequently, patients were categorized into early-onset AD (EOAD) and late-onset AD (LOAD) groups based on age. An arbitrary cut-off

age of 65 years was used, with early onset defined as the onset of symptoms before 65 years (onset < 65 years) and late-onset defined as the onset of symptoms at 65 years or later (onset ≥ 65 years).4,5 The majority of familial AD is early onset although late onset AD has also been reported.[13] Approximately 90% of AD is sporadic and the majority is late onset.[7] Familial EOAD usually follows an autosomal dominant pattern of inheritance and here symptoms appear in person's thirties, forties, or fifties and very rarely in the late twenties.[14] Data analysis was conducted using IBM Statistical Product and Service Solutions (SPSS) software, version 25, and the percentage frequencies of different types of pedigrees were calculated.

Results

Every participant, comprising all 37 individuals, received an AD diagnosis from a designated neurologist following an assessment of clinical symptoms, imaging reports, and MMSE scores. On average, the AD patients were diagnosed at the age of 70.09 years, with the majority (70.3%) being 65 years of age or older [Table 1].

Table 1. Age at diagnosis of the AD patients (n = 37)

Age at diagnosis (years)	% (n)*	Mean ± SD**
30-64	29.7 (11)	
≥ 65	70.3 (26)	70.09 ± 8.69

* %, percentage, n, number

** SD, standard deviation

Within the group of 37 clinically diagnosed AD patients, 27% (10 individuals) were identified as having familial AD, while the remaining 73% (27 individuals) had sporadic AD.

Among the ten familial AD patients, 70% (7) patients had EOAD. All of the familial EOAD patients had affected relatives in more than one generation, equally affected males and females, as shown in Figure 1. Regarding zygosity, 29% (2) patients had a heterozygous state, as shown in Figure 1. Males and females were equally inheriting the gene, an abnormal gene from one parent can cause the disease. Among the familial EOAD patients, female to male, female to female, male to female, male to male, all types of transmission were seen. Out of seven patients, 29% (2) patients had female to male transmission, as shown in Figure 1 and 14% (1) patients had female to female transmission (Figure 1).

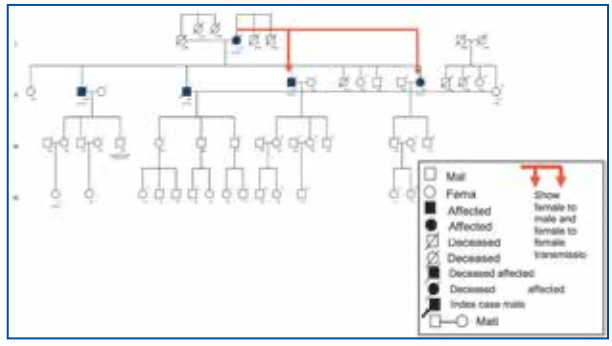

Figure 1. Pedigree of a familial EOAD patient. Note the presence of multiple generation involvement, heterozygous state, female to male transmission and female to female transmission.

Male to male transmission was present in 14% (1) patients and 14% (1) patients had male to female transmission, as shown in Figure 2.

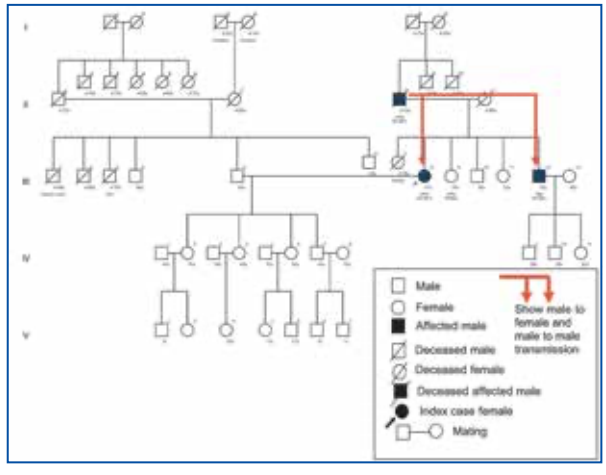

Figure 2. Pedigree of a familial EOAD patient. Note the presence of multiple generation involvement, male to male transmission and male to female transmission.

Out of ten familial AD patients, 30% (3) were found as LOAD patients. Among the three familial LOAD, 67% (2) patients had affected relatives in multiple generations and the affected parent transmitted the abnormal gene to the children, as shown in Figure 3. Regarding zygosity, 33% (1) patient had a heterozygous state, as shown in Figure 3 and only 33% (1) patients had affected relative in a single generation.

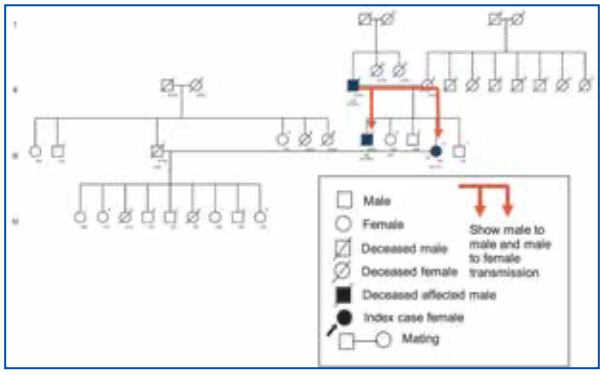

Figure 3. Pedigree of a familial LOAD patient. Note the presence of multiple generation involvement, heterozygous state, male to male transmission and male to female transmission.

The majority of the AD patients i.e., 73% (27) have no family history of AD hence these are sporadic AD. Only the affected person came as an index case as shown in Figure 4. Among those sporadic AD patients, about 85.19% (23) patients had LOAD and the remaining 14.81% (4) had EOAD as shown in Figure 5.

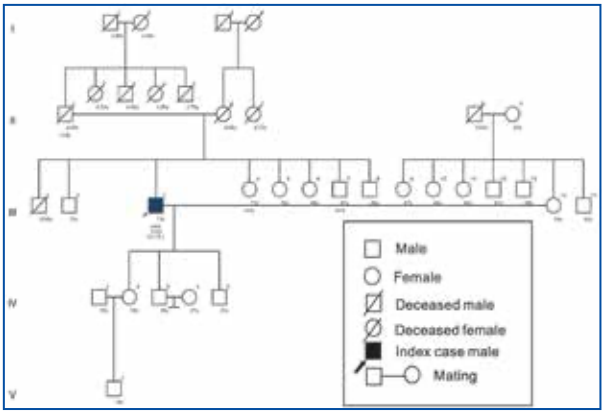

Figure 4. Pedigree of a sporadic AD (LOAD) patient. Note only index case is affected.

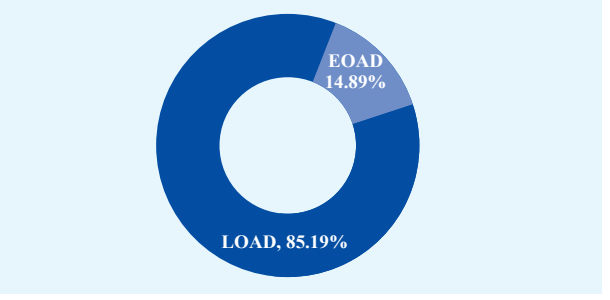

Figure 5. Percentage frequency distribution of sporadic AD patients (n= 27).

In this research, most of the patients i.e., 83.78% (31) had associated comorbidities like coronary heart disease, cerebrovascular disease, diabetes mellitus, hypertension, hypercholesterolemia. It is noticeable that, among 83.78% (31) patients, 51.35% (19) patients had hypertension followed by 43.24% (16) having diabetes mellitus. Only 10.81% (4) patients had hypercholesterolemia (Table 2).

Table 2. Comorbidity of the AD patients (n = 37)

Comorbidity	% (n)*
Absent	16.21% (6)
Present	83.78% (31)
Coronary heart disease	18.92% (7)
Cerebrovascular disease	35.13% (13)
Diabetes mellitus	43.24% (13)
Hypertension	51.35% (19)
Hypercholesterolemia	10.81% (4)

Discussion

The present research was carried out on adult Bangladeshi AD patients. As far as researcher knowledge, it is the first report on pedigree analysis of adult Bangladeshi AD patients in Bangladesh.

This research found that 70.3% of the AD patients were at or above 65 years age group. Age is the most recognized risk factor for AD. AD affects the majority of people over the age of 65. As a person matures past 65, their risk of developing Alzheimer's increases.[12,15]

The results of this research revealed that 27% of the AD cases were familial, whereas 73% were sporadic. Within the familial cases, a significant proportion (70%) had EOAD, suggesting a stronger genetic component, consistent with other studies that have found a higher genetic predisposition in EOAD compared to LOAD. The autosomal dominant pattern observed in familial cases aligns with findings from prior research, indicating that such inheritance could lead to earlier disease onset and more severe progression.[16] In this study, EOAD appears more prevalent, especially within the familial AD subset may be due small sample size and convenient sampling technique that may exclude the centers would have more LOAD patients.

The prevalence of LOAD being higher in sporadic cases (85.19%) highlights the potential involvement of non-genetic factors such as environmental influences and lifestyle choices in the pathogenesis of LOAD. This is

supported by research suggesting that sporadic cases often result from a complex interplay of genetics with modifiable risk factors, such as diet, physical activity, and exposure to environmental toxins.[17]

Positive family history with affected relatives in two or more generations is one of the criteria for dominant disease.[18] All the EOAD patients found in the present research have this criterion. In dominant disease, both male and female have an equal chance to become affected.[19] Five EOAD patients (71%) meet this criterion. If one parent has the affected gene, able to affect their offspring. Transmission by both male and female is another criterion of autosomal dominant disease. In the present research, two (29%) patients had female to male transmission, one (14%) patient had female to female transmission and male to male transmission was present in 14% (1) patients and one patient (14%) had male to female transmission. Every affected person had an affected parent but this may not be found in case of early death of any one parent.[18,19] Four patients (57%) in the present research had a history of early death of parents having comorbidity of the disease which indicates the parent's history of onset of disease may be missed here. Goldman et al. state that "families with autosomal dominant Alzheimer's disease have disease in at least three members through two or more generations, with two of the individuals being first-degree relatives of the third." In the present research, six EOAD patients (86%) meet the criteria of Autosomal dominant AD.[20] Campion et al.[21] found 20.83% autosomal dominant AD in their research. According to Goldman et al. Familial EOAD that follows autosomal dominant pattern of inheritance occurs mainly by mutations in one of the three genes, amyloid precursor protein (APP) or presenilin 1 (PSEN1) or presenilin 2 (PSEN2)[20]. Due to budget limitation, the genetic portion was kept for further research.

However, the finding that familial EOAD often involves more than one generation supports the notion of a strong genetic influence, which is critical for developing targeted genetic counseling and intervention strategies. By identifying patterns of inheritance and the specific ages at onset, healthcare professionals can better predict and manage the disease in high-risk families.[22]

Out of ten familial AD, 30% (3) were found as LOAD patients in the present research. Among three familial LOAD, one (33%) patient had affected relatives in multiple generations and the affected parent transmitted the abnormal gene to the children which meets the criteria of an autosomal dominant disease stated by Goldman et al.[19]. One patient (33%) had affected relatives in a single generation which does not match with the criteria for autosomal dominant disease. So, it can be said that out of ten familial AD, the present research found a total of seven (70%) patients who have fulfilled the criteria of autosomal dominant inheritance.

The present research found 73% sporadic cases. Among them, most of the patients (85.19%) had LOAD and only 14.81% (4) had EOAD. According to Goldman et al., sporadic AD accounts for 75% of total AD patients and most of them are LOAD.[19] Most of the sporadic AD patients (85%) had comorbidities like coronary heart disease, cerebrovascular disease, diabetes mellitus, hypertension and hypercholesterolemia. The most likely cause of sporadic AD may be molecular alterations (methylation, oxidative damage) in specific genes, which, in the lack of an efficient repair system in an aging individual, may manifest as a degenerative disease like AD.[23]Among the reported comorbidities, hypertension is the most frequent comorbidity found in AD patients. The present research found 51.35% of patients had hypertension. Another study in Bangladesh showed that hypertension was present in 49% of AD patients.[24] High frequency of hypertension is detected in our country may be due to lack of exercise and dietary habit i.e., more carbohydrate intake, high salt intake etc. The high incidence of comorbid conditions such as hypertension and diabetes among the AD patients, particularly those with LOAD, underscores the need for a holistic approach to management that includes addressing these concurrent health issues. Prior studies have shown that these comorbidities can exacerbate AD symptoms and complicate management, thus identifying and treating them could significantly improve quality of life and disease outcomes.[25]

The study is notable for being the first to conduct a detailed pedigree analysis of AD patients in Bangladesh, offering valuable insights into the familial and sporadic forms of AD in this population. However, the use of a convenient sampling method and reliance on patient-reported histories may limit the generalizability and accuracy of the findings. The lack of detailed brain imaging and

genetic testing for all affected family members also restricts the ability to fully elucidate inheritance patterns. Despite these limitations, the study underscores the importance of pedigree analysis in distinguishing between different types of AD and highlights the need for comprehensive genetic and medical evaluations to improve early diagnosis and personalized interventions.

Conclusion

The findings from this study underscore the significant impact of pedigree analysis in the context of Alzheimer's Disease (AD) management. Identifying familial patterns, particularly in early-onset cases, equips genetic counselors and healthcare providers with vital information for advising patients and their families. This knowledge facilitates early diagnosis, proactive intervention, and personalized care strategies, ultimately enhancing disease management. The implications of this research are especially relevant for improving AD outcomes in Bangladesh, potentially easing the burden on patients, families, and the healthcare system.

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