Observational Study

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Amyotrophic lateral sclerosis and neurodegenerative diseases

A Mendelian randomization study

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Abstract

In this study, we used the Mendelian randomization (MR) method to systematically examine whether there is a bidirectional causal relationship between amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). We analyzed data from 6,44,924 participants using MR to evaluate causality. We employed inverse variance weighted and MR-Egger regression tests for MR analysis. Additionally, we performed sensitivity analyses using the MR-Egger test and Mendelian Randomization Pleiotropy RESidual Sum and Outlier. The inverse variance weighted analysis found no evidence of a risk effect between ALS and the neurodegenerative diseases AD, PD, FTD, MSA, and DLB. However, the MR-Egger analysis showed that both AD (odds ratio: 1.079, 95% confidence interval: 1.017–1.145, $P = .029$) and PD (odds ratio: 1.210, 95% confidence interval: 1.046–1.401, $P = .020$) have a risk effect on ALS, indicating that AD and PD increase the risk of ALS. Our MR analysis suggests that AD and PD may have a potential causal relationship with ALS. Conversely, ALS does not appear to have a causal relationship with the other neurodegenerative diseases examined (FTD, MSA, DLB).

Abbreviations: AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, GWAS = genome-wide association study, IVW = inverse variance weighted, KANSL1 = KAT8 regulatory non-specific lethal complex subunit 1, MR = Mendelian randomization, MSA = multiple system atrophy, OR = odds ratio, PD = Parkinson's disease, SNPs = single nucleotide polymorphisms, TDP-43 = TAR-DNA binding protein of 43 kDa.

Keywords: Alzheimer's disease, amyotrophic lateral sclerosis, dementia with Lewy bodies, frontotemporal dementia, Mendelian randomization study, multiple system atrophy, Parkinson's disease

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a prevalent neurodegenerative disease marked by the progressive degeneration of motor neurons, ultimately leading to respiratory failure and death.[1,2] Currently, there is no specific treatment for ALS, and the prognosis remains poor, with a typical survival time ranging from 2 to 5 years.[3] This disease imposes a significant burden on patients and healthcare systems worldwide. Recent research has revealed that ALS-related damage extends beyond upper and lower motor neurons, also affecting other systems such as the extrapyramidal system, autonomic nervous system, and cerebellum. These findings indicate that ALS may share common pathological features with other neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), multiple system atrophy (MSA), and Lewy body dementia.[4,5]

ALS shares symptomatic, genetic, pathological, and pathogenic similarities with AD, PD, FTD, MSA, and dementia with Lewy bodies (DLB). Misfolded proteins in the central nervous system can induce oxidative stress, leading to mitochondrial dysfunction, impaired energy utilization, and the progression

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of diseases such as ALS, AD, PD, and MSA.[6,7] Protein aggregation is a prevalent pathological feature in neurodegenerative diseases, causing neuroinflammation and exacerbating protein aggregation, further contributing to conditions like ALS, AD, PD, and FTD.[8,9] Recent evidence indicates a moderate genetic overlap among ALS, AD, and PD. This includes lysosomal/autophagy dysfunction (e.g., GAK/TMEM175, recombinant granulin, KAT8 regulatory non-specific lethal complex subunit 1 [KANSL1]), neuroinflammation/immunity (TSPO-associated protein 1), oxidative stress (glutathione peroxidase 3, KANSL1), and DNA damage response (NEK1) pathways, which are implicated in the diagnostic processes of various neurodegenerative diseases.[10] Additionally, microglia play a dual role: they protect by clearing pathological protein aggregates and contribute to neurodegeneration when excessive uptake of these aggregates impairs their phagocytic function, leading to neuroinflammation and neurodegenerative conditions, including ALS, AD, PD, FTD, MSA, and DLB.[11] Hippocampal dysfunction is associated with mental comorbidities and cognitive impairment in neurodegenerative diseases. The involvement of adult hippocampal neurogenesis in ALS, PD, DLB, and FTD suggests that the increased vulnerability of adult hippocampal neurogenesis to neurodegeneration may underlie hippocampal dysfunction during human aging, both physiologically and pathologically.[12]

Previous studies examining the associations between diseases have primarily utilized observational study designs. While well-designed randomized controlled trials are considered the gold standard for estimating causality between risk factors and diseases, traditional research methods often encounter challenges due to potential biases. In recent years, Mendelian randomization (MR) analysis has emerged as a powerful tool for exploring causal relationships between various diseases at the genetic level.[13–15] Genetic variants, fixed at birth and randomly distributed among individuals, allow MR analysis to effectively control for confounding factors. This method enables a more accurate assessment of potential causal relationships between ALS and other neurodegenerative diseases, such as AD, PD, FTD, MSA, and DLB, providing a scientific basis for developing prevention and treatment strategies.

In this study, we applied a 2-sample MR analysis using large-scale genome-wide association study (GWAS) data to uncover the causal effects of ALS on the risk of neurodegenerative diseases (AD, PD, FTD, MSA, DLB).

2. Materials and methods

2.1. Data sources and study design

In this study, we employed a 2-sample MR analysis using GWAS datasets for 6 neurodegenerative diseases: ALS, AD, PD, FTD, MSA, and DLB. These datasets were sourced from the IEU Open GWAS project, the GWAS Catalog, and various other consortia. The MR design must adhere to 3 key assumptions: genetic instruments must robustly predict the exposures of interest ($P < 5 \times 10^{-8}$); genetic instruments must be independent of potential confounding factors; and genetic instruments must influence outcomes solely through their effects on risk factors.[16]

2.2. Bidirectional 2-sample MR

To investigate a causal relationship between ALS and various neurodegenerative diseases, we conducted a 2-sample MR analysis following established guidelines. This approach aimed to evaluate the risk of ALS while controlling for biases from confounding factors and reverse causation. Our analysis utilized population-based cohort GWAS with the following sample sizes: ALS (N = 80,610), AD (N = 63,926), PD (N = 4,82,730), FTD (N = 3024), MSA (N = 8016), and DLB (N = 6618).

We selected single nucleotide polymorphisms (SNPs) based on the following criteria:

Minimal linkage disequilibrium, defined by a probability ($r^2 > 0.001$) and a maximum distance of 10,000 kb; adequate instrumental variable strength, with an F statistic > 10; we excluded SNPs that showed a significant correlation with the outcome ($P < 5e^{-5}$); to prevent reverse causation, we applied the MR Steiger filter for evaluation, utilizing the default threshold set by the "mr_steiger" function. We employed 2-sample MR to investigate the odds ratio (OR) between these 5 neurodegenerative diseases and ALS, with the goal of obtaining unbiased results.

2.3. Statistical analysis

We determined significant correlations using MR analysis with a threshold of $P < .05$. For sensitivity analysis, we employed methods including MR-Egger and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO). MR-Egger allowed us to assess heterogeneity and pleiotropy. We primarily utilized the inverse variance weighted (IVW) model, with the MR-Egger model serving as a supplementary method for sensitivity evaluation.[17–19] We conducted all statistical analyses using R (v4.2.3) and utilized software packages such as TwoSampleMR (v0.5.6) and MR-PRESSO (v1.0).

3. Results

3.1. Demographic characteristics of participants

Figure 1 illustrates the research process for MR. We selected 6,44,924 participants from the database based on specific inclusion and exclusion criteria. Table 1 presents basic demographic information about the participants, including age, gender, family history, and other relevant characteristics.

3.2. Results of bidirectional 2-sample MR analysis

We used 2-sample MR analysis to examine the causal effects between diseases, as summarized in Tables 2 and 3 and Figure 2. To investigate the causal relationship between ALS and neurodegenerative diseases (including AD, PD, FTD, MSA, and DLB), we applied the IVW and MR-Egger methods. The IVW results indicated no evidence of causality, either forward or reverse, between ALS and these neurodegenerative diseases. Notably, MR-Egger analysis revealed a nominally significant causal relationship between AD and ALS (OR = 1.079, 95% confidence interval : 1.017–1.145, $P = .029$), as well as between PD and ALS (OR = 1.210, 95% confidence interval: 1.046–1.401, $P = .020$).

3.3. Sensitivity analysis

To ensure the robustness of our results, we conducted a series of sensitivity analyses, including the IVW test, the MR-Egger test, and the MR-PRESSO test (Table 4). All P-values from the MR-Egger model were >.05, indicating the absence of horizontal pleiotropy. The causal effect estimates were consistent between the IVW and MR-Egger methods. Furthermore, we did not detect heterogeneity in the other analyses.

4. Discussion

This study reveals the causal effects of ALS and neurodegenerative diseases, including AD, PD, FTD, MSA, and DLB. Our findings indicate that AD and PD may contribute to the risk of developing ALS. Notably, AD, PD, and ALS share many clinical and pathophysiological features, such as lysosomal dysfunction, mitochondrial dysfunction, oxidative stress,

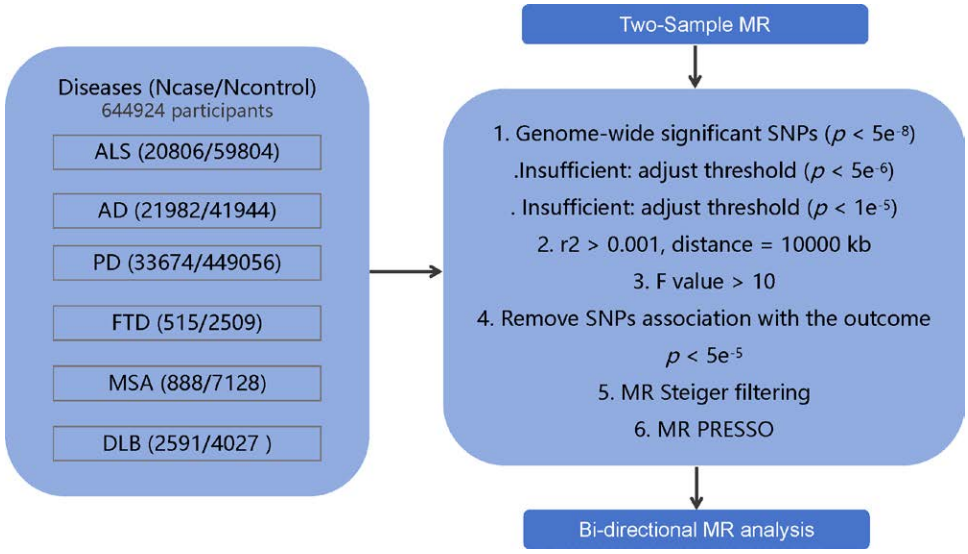

Figure 1. Flow chart of the research process. AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MR = Mendelian randomization, MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier, MSA = multiple system atrophy, PD = Parkinson's disease, SNPs = single nucleotide polymorphisms.

Table 1

Characteristics of the participants (N = 6,44,924).

	ALS	AD	PD	FTD	MSA	DLB
PubMed ID	29566793	30820047	31701892	20154673	38701790	33589841
Consortium	US, Italian, UK, French, Belgian	Europe	Europe	Europe	Europe, USA	Europe
	Cases	Cases	Cases	Cases	Cases	Cases
Female (%)	3433 (41.7)	ADGC, 8555 (59.3) CHARGE, 1438 (67.3) EADI, 1456 (65) GERAD, 2033 (64)	10,728 (57.62)	227 (44.3)	416 (47)	948 (37)
Mean age (SD/range)	59.8 (12.3)	ADGC, 71.1 (17.3) CHARGE, 82.6 (12) EADI, 75.4 (9.1) GERAD, 73.0 (0.2)	58.45 (7.20)	59.8 (9.8/28–89)	64 (38–91)	75 (11)
Bulbar-onset (%)	2202 (26.8)	/	/	/	/	/
Family history (%)	955 (11.6)	/	/	169 (42.7)	/	/
Clinically ascertained, n (%)	/	/	/	/	/	802 (31)
Pathologically diagnosed, n (%)	/	/	/	/	/	1789 (69)
Clinically probable MSA, n (%)	/	/	/	/	420 (47)	/
Definite MSA, n (%)	/	/	/	/	468 (53)	/
MSA-P, n (%)	/	/	/	/	202 (23)	/
MSA-C, n (%)	/	/	/	/	127 (14)	/
Not available, n (%)	/	/	/	/	559 (63)	/

AD = Alzheimer's disease, ADGC = Alzheimer's Disease Genetics Consortium, ALS = amyotrophic lateral sclerosis, CHARGE = genomic epidemiology consortium, DLB = dementia with Lewy bodies, EADI = European Alzheimer's Disease Initiative, FTD = frontotemporal dementia, GERAD = Genetic and Environmental Risk in AD/Defining Genetic, MSA = multiple system atrophy, MSA-C = multiple system atrophy of cerebellar type, MSA-P = parkinsonian variant of multiple system atrophy, PD = Parkinson's disease, SD = standard deviation.

and neuroinflammation, all influenced by environmental factors.[6,8,9,20–24] Approximately 10% to 15% of ALS cases exhibit associated AD pathology.[25]

The TAR-DNA binding protein of 43 kDa (TDP-43), encoded by the TARDBP gene, is an endo-nuclear protein involved in RNA splicing, transport, and stabilization, thereby regulating gene expression. TDP-43 inclusion bodies, a hallmark of ALS, are found in up to 57% of Alzheimer's disease cases, most commonly in marginal distributions. These findings strongly suggest that TDP-43 pathology is a common component in both AD and ALS.[26]

A recent study employed local genetic correlation to identify a common locus (human leukocyte antigen) for AD, ALS, and PD, successfully quantifying the genetic overlap among these 3 diseases.[27] The endoplasmic reticulum plays a crucial role in maintaining protein homeostasis through the unfolded protein response, which is strongly activated in most neurodegenerative diseases. Two major UPR signaling pathways, mediated by IRE1α and ATF6, activate overlapping and disease-specific patterns of IRE1α-XBP1 and ATF6 target genes in both AD and ALS.[28]

A recent genome-wide association study identified 11 common genetic risk sites shared by PD and ALS. These genes implicate lysosomal/autophagy dysfunction (GAK/TMEM175, recombinant granulin, KANSL1), neuroinflammation/immunity (TSPO-associated protein 1), oxidative stress (glutathione peroxidase 3, KANSL1), and DNA damage response (NIMA-related kinase 1) as diagnostic processes for both PD and ALS.[10] An NGS study further confirmed the potential role of PD-related genes as risk modifiers in the pathogenesis of ALS.[29]

Table 2

Causal effects of neurodegenerative diseases and ALS (IVW).

Exposure	Outcome	*b*	SE	OR [95% CI]	*P*
ALS	AD	0.023	0.080	1.024 [0.875–1.197]	.770
ALS	PD	0.059	0.073	1.061 [0.920–1.223]	.418
ALS	DLB	0.103	0.162	1.109 [0.806–1.524]	.526
ALS	MSA	–0.076	0.263	0.927 [0.554–1.551]	.772
ALS	FTD	0.207	0.571	1.230 [0.402–3.764]	.717
AD	ALS	0.044	0.023	1.045 [0.999–1.092]	.053
PD	ALS	0.053	0.028	1.054 [0.998–1.113]	.057
DLB	ALS	0.019	0.033	1.020 [0.956–1.087]	.556
MSA	ALS	0.040	0.052	1.041 [0.941–1.152]	.437
FTD	ALS	0.026	0.017	1.026 [0.993–1.061]	.122

AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, CI = confidence interval, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, IVW = inverse variance weighted, MSA = multiple system atrophy, OR = odds ratio, PD =Parkinson's disease.

Table 3

Causal effects of neurodegenerative diseases and ALS (MR-Egger).

Exposure	Outcome	*b*	SE	OR [95% CI]	*P*
ALS	AD	–0.132	0.239	0.877 [0.549–1.400]	.679
ALS	PD	0.088	0.178	1.091 [0.770–1.547]	.657
ALS	DLB	0.172	0.413	1.187 [0.529–2.666]	.705
ALS	MSA	0.633	0.931	1.883 [0.303–11.678]	.620
ALS	FTD	–2.937	5.510	0.053 [1.083–2597.348]	.688
AD	ALS	0.076	0.030	1.079 [1.017–1.145]	.029
PD	ALS	0.191	0.074	1.210 [1.046–1.401]	.020
DLB	ALS	0.009	0.065	1.009 [0.889–1.145]	.899
MSA	ALS	NA	NA	NA	NA
FTD	ALS	0.026	0.071	1.027 [0.893–1.180]	.726

AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, CI = confidence interval, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MR = Mendelian randomization, MSA = multiple system atrophy, NA = not available, OR = odds ratio, PD = Parkinson's disease.

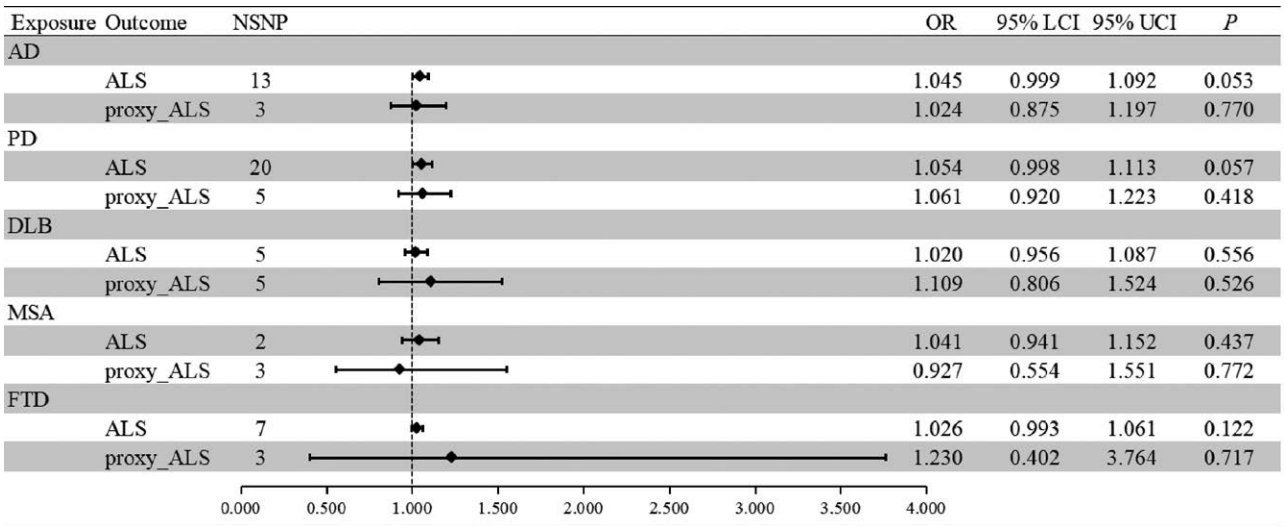

Figure 2. Causal effects of neurodegenerative diseases on ALS (IVW). AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, IVW = inverse variance weighted, LCI = lower confidence interval, MSA = multiple system atrophy, NSNP = number of single nucleotide polymorphisms, OR = odds ratio, PD = Parkinson's disease, UCI = upper confidence interval.

Epidemiological studies indicate that offspring of PD patients have an increased risk of developing ALS,[30] and up to 30% of ALS patients may develop Parkinsonian features.[31] These findings align with our results, suggesting that PD may increase the risk of ALS. The largest GWAS in ALS patients has established a genetic link between the pathogenesis of ALS and PD, revealing site-specific patterns of shared genetic risk for the diseases.[32] This phenomenon likely arises from the genetic overlap among different degenerative diseases. The C9Orf72 gene, the most common gene associated with ALS, can manifest as either typical or atypical PD.[33,34]

One case study[35] reported that 5 AD patients all developed ALS, with 1 autopsied patient showing characteristic lesions of both diseases. This study suggests that the ALS-AD phenotype may be an underexplored specific entity. Elevated plasma levels of threonine 181 phosphorylated tau protein (p-tau181) have been identified as a highly accurate marker of AD. Recently, new evidence[36] found elevated plasma p-tau181 in patients with

Table 4

Sensitivity analysis of causal relationship between neurodegenerative diseases and ALS.

Exposure	Outcome	Inverse variance weighted (*Q*)	Inverse variance weighted (*Q_P*)	MR-Egger (*Q*)	MR-Egger (*Q_P*)	MR-PRESSO (*P*)
ALS	AD	0.772	.680	0.297	.586	.147
ALS	PD	3.015	.555	2.984	.394	.565
ALS	DLB	4.608	.330	4.555	.207	NA
ALS	MSA	1.534	.464	0.904	.342	NA
ALS	FTD	0.864	.649	0.535	.465	NA
AD	ALS	12.442	.411	9.970	.533	NA
PD	ALS	22.672	.252	18.622	.415	.257
DLB	ALS	10.768	.029	10.629	.014	.136
MSA	ALS	1.811	.178	NA	NA	NA
FTD	ALS	7.608	.268	7.608	.179	.257

AD = Alzheimer's disease, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MR = Mendelian randomization, MR-PRESSO = Mendelian Randomization Pleiotropy RESidual Sum and Outlier, MSA = multiple system atrophy, NA = not available, PD = Parkinson's disease.

ALS, indirectly suggesting a causal relationship between AD and ALS. Previous studies also discovered that relatives of ALS patients have a significantly higher risk of dementia compared to control groups, and relatives of familial ALS patients have a higher risk of PD.[37]

Our research indicates that ALS may not have a causal relationship with neurodegenerative diseases (FTD, MSA, DLB). However, relevant studies have shown that abnormal accumulation of TDP-43 has been found in both ALS and FTD,[38–40] and there is also pathological evidence of TDP-43 in MSA and DLB.[41,42] The genetic overlap phenomenon of C9Orf72 between ALS and FTD has been confirmed.[43,44] This evidence suggests that our research may have limitations. Furthermore, our study confirmed the evidence of the causal relationship between AD and PD on ALS. However, unfortunately, no evidence of the causal relationship between ALS on AD and PD was found. This might be due to the existence of undetected confounding factors.

We speculate that MR analysis is merely a method for analyzing the causal relationship between exposure and outcome. It is more helpful in determining the association's direction than quantifying the association's size, and perhaps cannot completely replace clinical trials in the objective world. Although we conducted a sensitivity analysis to assess the potential impact of pleiotropy, the residual confounding factors could not be excluded entirely. Since the dataset mainly relies on large-sample GWAS databases, and these data are mostly from the European population, the research conclusions may not be directly generalized to the Asian population or other non-European populations. This problem of underrepresentation of the population may limit the general applicability of the research results. Therefore, we expect that more subsequent studies will be needed for verification and to deeply explore the specific biological mechanisms of the possible causal relationship between ALS and neurodegenerative diseases. Our research also suggests that the shared genetic or pathological characteristics among ALS, AD and PD may provide information for targeted therapeutic approaches or risk stratification in the clinical setting.

5. Conclusion

This is the 1st MR study to investigate the causal relationship between ALS and other neurodegenerative diseases, including AD, PD, FTD, MSA, and DLB. Our MR analysis supports the hypothesis that AD and PD increase the incidence of ALS.

Author contributions

Conceptualization: Chaofang Lei, Jiaxu Chen, Zhigang Chen, Le Xie.
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Writing – review & editing: Chaofang Lei, Le Xie.

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