Other Dementias: A Comprehensive Review of Normal Pressure Hydrocephalus, Creutzfeldt–Jakob Disease, Huntington's Disease, HIV-Associated Dementia, and Toxin- and Infection-Related Cognitive Disorders

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Abstract

Background. Although Alzheimer's disease and vascular dementia account for the majority of dementia cases worldwide, several less common disorders collectively contribute substantially to cognitive impairment, disability, caregiver burden, and healthcare utilization. These conditions include normal pressure hydrocephalus (NPH), Creutzfeldt–Jakob disease (CJD), Huntington's disease (HD), HIV-associated dementia (HAD), and toxin- and infection-related dementias. Unlike many common neurodegenerative dementias, several of these disorders are potentially reversible or amenable to disease-specific interventions, making early recognition clinically important.

Objective. To provide a comprehensive review of the epidemiology, pathophysiology, clinical manifestations, diagnosis, management, prognosis, and future directions of major non-Alzheimer dementias encountered in neurological and geriatric practice.

Methods. A narrative review approach was employed using contemporary evidence from peer-reviewed literature, international guidelines, and major neurology, infectious disease, and dementia references. Emphasis was placed on diagnostic advances, biomarker development, neuroimaging findings, and emerging therapeutic strategies.

Results. NPH remains one of the most treatable causes of cognitive decline, with cerebrospinal fluid diversion producing meaningful improvement in appropriately selected patients. CJD represents a rapidly progressive prion disease characterized by severe neurological deterioration and poor survival. HD is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansion within the huntingtin gene and serves as a model for gene-targeted therapeutic development. HIV-associated dementia has become less common in the era of combination antiretroviral therapy but continues to contribute significantly to morbidity. Toxin- and infection-related dementias encompass a heterogeneous group of disorders in which early diagnosis may prevent irreversible neurological injury.

Conclusions. The biological diversity of these disorders highlights the need for individualized diagnostic and therapeutic approaches. Advances in biomarkers, neuroimaging, genetics, artificial intelligence, and precision medicine are expected to transform the evaluation and management of these conditions. Improved recognition of potentially reversible causes of dementia remains essential for optimizing patient outcomes.

Keywords: Dementia; Normal Pressure Hydrocephalus; Creutzfeldt–Jakob Disease; Huntington's Disease; HIV-Associated Dementia; Neurocognitive Disorders; Prion Disease; Cognitive Impairment; Biomarkers; Precision Medicine.

Overview

Introduction

Dementia is a clinical syndrome characterized by acquired cognitive decline sufficient to interfere with independence in daily functioning. According to the World Health Organization, more than 55 million individuals worldwide are currently living with dementia, a number expected to increase substantially as populations age (World Health Organization [WHO], 2023). Although Alzheimer's disease and vascular dementia account for most cases, a variety of less common neurological, infectious, genetic, and toxic disorders contribute significantly to the global burden of cognitive impairment.

The term "other dementias" encompasses a heterogeneous group of disorders that differ markedly in etiology, pathophysiology, clinical course, and treatment responsiveness. Some conditions are progressive neurodegenerative disorders associated with irreversible neuronal loss, whereas others may stabilize or improve if diagnosed and treated early. Recognition of these distinctions is essential because therapeutic opportunities and prognostic implications vary considerably among disease categories.

This review focuses on five major groups of non-Alzheimer dementias: normal pressure hydrocephalus, Creutzfeldt–Jakob disease, Huntington's disease, HIV-associated dementia, and toxin- or infection-related dementias. Together, these conditions illustrate the diverse biological mechanisms capable of producing cognitive decline.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus is a potentially reversible neurological disorder characterized by enlargement of the cerebral ventricles despite normal or intermittently elevated cerebrospinal fluid (CSF) pressure. The classic clinical triad consists of gait disturbance, cognitive impairment, and urinary dysfunction (Nakajima et al., 2021). Among these manifestations, gait impairment is typically the earliest and most prominent symptom.

NPH is particularly important because it represents one of the few treatable causes of dementia. Appropriate patient selection for ventriculoperitoneal shunting may result in significant improvement in mobility, functional status, and quality of life. However, diagnosis remains challenging because symptoms often overlap with those of Alzheimer's disease, vascular dementia, and Parkinsonian syndromes.

Creutzfeldt–Jakob Disease

Creutzfeldt–Jakob disease is a rare but devastating prion disorder characterized by rapidly progressive cognitive decline, motor dysfunction, and death. The disease results from abnormal folding of the cellular prion protein into a pathogenic isoform capable of inducing further protein misfolding and neurodegeneration (Hermann et al., 2021).

Unlike most dementias, which progress over years, CJD often evolves over weeks to months. Clinical manifestations commonly include dementia, myoclonus, cerebellar dysfunction, visual disturbances, pyramidal signs, and akinetic mutism during advanced stages. The introduction of real-time quaking-induced conversion (RT-QuIC) assays has substantially improved diagnostic accuracy and facilitated earlier recognition of prion disease.

Huntington's Disease

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by expansion of CAG trinucleotide repeats within the huntingtin (HTT) gene on chromosome 4. The disease is characterized by a combination of motor, cognitive, and psychiatric manifestations (McColgan & Tabrizi, 2018).

Although chorea is the most recognizable clinical feature, cognitive impairment and behavioural disturbances often contribute more substantially to long-term disability. Progressive degeneration of the striatum and associated neural networks ultimately results in severe functional dependence. Importantly, Huntington's disease has become a major focus of precision medicine research because its genetic basis is clearly defined, creating opportunities for targeted therapeutic interventions.

HIV-Associated Dementia

HIV-associated dementia represents the most severe end of the spectrum of HIV-associated neurocognitive disorders (HAND). Prior to the widespread availability of combination antiretroviral therapy (ART), HAD was a common neurological complication of advanced HIV infection. Although its incidence has declined significantly, milder forms of neurocognitive impairment remain prevalent among people living with HIV (Nightingale et al., 2023).

The pathogenesis of HAD involves chronic neuroinflammation, immune activation, viral persistence within the central nervous system, and indirect neuronal injury. Clinical manifestations typically include psychomotor slowing, executive dysfunction, impaired attention, and behavioural changes. Early diagnosis and optimization of antiretroviral therapy remain essential components of management.

Toxin- and Infection-Related Dementias

A variety of environmental toxins and infectious agents can produce cognitive impairment and dementia. Toxic causes include chronic alcohol misuse, heavy metal exposure, carbon monoxide poisoning, and certain occupational or environmental neurotoxins. Infectious causes include neurosyphilis, tuberculosis, cryptococcosis, progressive multifocal leukoencephalopathy, Whipple disease, and other central nervous system infections.

These conditions are clinically important because many are partially or completely reversible when recognized early. Consequently, evaluation of potentially treatable causes remains a fundamental component of every dementia assessment. Failure to identify such disorders may result in preventable neurological disability and unnecessary progression of cognitive decline.

Comparative Features of Major Other Dementias

Table 1. Major Characteristics of Selected Other Dementias

Disorder	Primary Mechanism	Typical Progression	Potential Reversibility
Normal Pressure Hydrocephalus	CSF circulation dysfunction	Months–years	Moderate to high
Creutzfeldt–Jakob Disease	Prion protein misfolding	Weeks–months	None
Huntington's Disease	HTT gene mutation	Years–decades	None
HIV-Associated Dementia	Neuroinflammation and viral injury	Variable	Partial
Toxin-Related Dementias	Neurotoxic exposure	Variable	Often partial
Infection-Related Dementias	CNS infection	Variable	Often substantial

Significance of Early Recognition

Despite their relative rarity compared with Alzheimer's disease, these disorders hold disproportionate clinical importance because several are potentially treatable, require specific management strategies, or have unique implications for patients and families. Early diagnosis can facilitate timely intervention, improve functional outcomes, guide prognostic counseling, and enable access to disease-specific therapies.

Advances in neuroimaging, molecular diagnostics, genetic testing, and biomarker research are increasingly allowing clinicians to identify these disorders at earlier stages than previously possible. As a result, the distinction between neurodegenerative, infectious, toxic, and potentially reversible causes of dementia has become increasingly important in contemporary neurological practice.

Etiology and Epidemiology

Etiology
The disorders discussed in this review represent diverse pathogenic mechanisms leading to cognitive impairment and dementia. Unlike Alzheimer's disease, which is primarily characterized by amyloid-β and tau pathology, these conditions arise from disturbances in cerebrospinal fluid dynamics, protein misfolding, genetic mutations, chronic viral infection, toxic exposures, or direct central nervous system (CNS) infections. Understanding their etiological basis is essential because treatment options, prognosis, and opportunities for prevention vary considerably among disorders.

Normal Pressure Hydrocephalus
Normal pressure hydrocephalus (NPH) results from impaired cerebrospinal fluid (CSF) circulation and absorption, leading to progressive ventricular enlargement despite normal or intermittently elevated CSF pressure (Nakajima et al., 2021). The condition is traditionally classified as either idiopathic or secondary.
Idiopathic normal pressure hydrocephalus (iNPH) accounts for most cases and occurs without an identifiable precipitating event. Although the exact pathogenesis remains incompletely understood, current evidence suggests dysfunction of CSF resorption pathways, altered intracranial compliance, impaired glymphatic clearance, and age-related vascular changes contribute to disease development.

Secondary NPH occurs following conditions that disrupt normal CSF dynamics, including:
- Subarachnoid hemorrhage
- Traumatic brain injury
- Meningitis
- Intracranial surgery
- Other inflammatory CNS disorders

The resulting impairment of CSF circulation leads to ventricular dilation and secondary disruption of periventricular white matter pathways involved in gait, cognition, and bladder control.

Creutzfeldt–Jakob Disease
Creutzfeldt–Jakob disease (CJD) is a transmissible spongiform encephalopathy caused by the conformational conversion of the normal cellular prion protein (PrP^C) into the pathogenic isoform (PrP^Sc), resulting in the accumulation of protease-resistant prion aggregates and progressive neurodegeneration. (Hermann et al., 2021).

Four major forms of CJD are recognized:

Sporadic CJD
Sporadic CJD accounts for approximately 85–90% of cases and arises without an identifiable cause. The initiating event remains uncertain but is believed to involve spontaneous conformational alteration of normal prion protein.

Genetic CJD
Approximately 10–15% of cases are associated with pathogenic mutations in the prion protein gene (PRNP). More than 50 disease-associated mutations have been identified, producing variable clinical phenotypes and disease durations.

Iatrogenic CJD
Rare cases have occurred following exposure to contaminated biological materials, including:
- Human growth hormone preparations
- Dura mater grafts
- Corneal transplantation
- Neurosurgical instruments

Variant CJD
Variant CJD is associated with exposure to bovine spongiform encephalopathy ("mad cow disease") and demonstrates distinct clinicopathological characteristics.

Huntington's Disease
Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by expansion of a CAG trinucleotide repeat within exon 1 of the huntingtin (HTT) gene located on chromosome 4p16.3 (McColgan & Tabrizi, 2018).

Normal individuals typically possess fewer than 27 CAG repeats, whereas pathogenic expansions usually contain 40 or more repeats. Expanded repeats produce an abnormal huntingtin protein that undergoes aggregation, disrupts intracellular signaling pathways, impairs mitochondrial function, and ultimately causes neuronal death, particularly within the striatum.

A characteristic feature of HD is genetic anticipation, whereby larger repeat expansions are transmitted to subsequent generations, often resulting in earlier disease onset and more severe clinical manifestations.

HIV-Associated Dementia
HIV-associated dementia (HAD) represents the most severe manifestation of HIV-associated neurocognitive disorders (HAND). The disorder results not from direct neuronal infection but from indirect neuronal injury mediated by infected macrophages, microglia, chronic immune activation, and persistent neuroinflammation (Nightingale et al., 2023).

Mechanisms contributing to cognitive impairment include:
- Chronic neuroinflammatory activation
- Release of neurotoxic cytokines
- Synaptic dysfunction
- White matter injury
- Blood-brain barrier disruption
- Persistent viral reservoirs within the CNS

The widespread implementation of combination antiretroviral therapy (ART) has significantly altered disease epidemiology and reduced the incidence of severe dementia.

Toxin-Related Dementias
Numerous environmental and occupational toxins have been implicated in cognitive impairment. The severity of neurological injury depends upon exposure duration, cumulative dose, patient susceptibility, and timeliness of intervention.

Major causes include:
Alcohol
Chronic alcohol misuse may result in:
- Alcohol-related dementia
- Wernicke encephalopathy
- Korsakoff syndrome

through direct neurotoxicity, nutritional deficiency, and disruption of neuronal metabolism (Zis et al., 2021).

Heavy Metals
Neurotoxic metals associated with cognitive decline include:
- Lead
- Mercury
- Arsenic
- Manganese

These substances promote oxidative stress, mitochondrial dysfunction, and neuronal injury.

Carbon Monoxide
Carbon monoxide poisoning produces cerebral hypoxia and delayed neuropsychiatric sequelae, which may include persistent cognitive impairment and executive dysfunction.

Infection-Related Dementias
A wide range of infectious diseases can affect cognitive function either directly through CNS invasion or indirectly through inflammatory and vascular mechanisms.

Important causes include:
Neurosyphilis
Untreated infection with Treponema pallidum may produce progressive cognitive decline, personality change, psychiatric symptoms, and dementia.

Tuberculosis
Tuberculous meningitis may cause chronic cognitive impairment through meningeal inflammation, hydrocephalus, cerebral infarction, and parenchymal injury.

Cryptococcal Infection
Cryptococcal meningoencephalitis remains an important cause of cognitive dysfunction among immunocompromised individuals.

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) results from reactivation of the John Cunningham (JC) virus and causes demyelination of cerebral white matter.

Whipple Disease
Although rare, Whipple disease may produce cognitive decline, psychiatric symptoms, and movement disorders.

Epidemiology
The epidemiological characteristics of these disorders differ substantially. Some conditions are relatively common among older adults, whereas others remain rare but clinically significant because of their severity, treatability, or unique diagnostic implications.

Normal Pressure Hydrocephalus
NPH is increasingly recognized as an important cause of potentially reversible cognitive decline in older adults. Population-based studies estimate prevalence rates ranging from 0.2% to 2.9% among individuals over 65 years of age, with prevalence increasing markedly in advanced age groups (Nakajima et al., 2021).

Many experts believe NPH remains underdiagnosed because symptoms overlap with more common neurodegenerative disorders. Improved neuroimaging and greater awareness have contributed to increasing recognition worldwide.

Creutzfeldt–Jakob Disease
CJD is rare but occurs globally. The annual incidence remains remarkably consistent across populations at approximately 1–2 cases per million persons per year (Hermann et al., 2021).

Sporadic CJD typically presents between 60 and 70 years of age. Variant CJD remains exceedingly uncommon following implementation of public health measures designed to control bovine spongiform encephalopathy.

Huntington's Disease
The prevalence of HD varies considerably by geographic region and ancestry. Rates are highest in populations of European descent, where prevalence generally ranges from 5 to 14 cases per 100,000 individuals (McColgan & Tabrizi, 2018).

Lower prevalence rates have historically been reported in Asian and African populations, although improved genetic testing has increased recognition globally.

HIV-Associated Dementia
Before the introduction of effective ART, HAD affected approximately 15–30% of individuals with advanced HIV infection. Although severe dementia has become less common, milder forms of HIV-associated neurocognitive impairment continue to affect a substantial proportion of patients living with HIV (Nightingale et al., 2023).
The burden is greatest in regions with high HIV prevalence and limited healthcare resources.

Toxin- and Infection-Related Dementias
Reliable epidemiological estimates are challenging because these conditions encompass numerous etiologies and frequently remain under-recognized.

The prevalence of toxin-related cognitive impairment varies according to:
- Occupational exposures
- Environmental regulations
- Alcohol consumption patterns
- Public health infrastructure

Similarly, infection-related dementias demonstrate considerable geographic variability. Neurosyphilis remains more common in regions with limited access to screening and treatment, whereas tuberculosis-related cognitive impairment is concentrated in countries with high tuberculosis prevalence.

Comparative Epidemiology

Table 2. Global Epidemiological Characteristics of Major Other Dementias

Disorder	Estimated Prevalence/Incidence	Typical Age at Onset
Normal Pressure Hydrocephalus	0.2–2.9% of adults >65 years	>60 years
Creutzfeldt–Jakob Disease	1–2 cases per million/year	60–70 years
Huntington's Disease	5–14 per 100,000 (Western populations)	30–50 years
HIV-Associated Dementia	Variable; reduced in ART era	Any age with HIV
Toxin-Related Dementias	Variable	Exposure dependent
Infection-Related Dementias	Variable	Infection dependent

Clinical Implications
The epidemiological diversity of these disorders highlights the importance of maintaining a broad differential diagnosis when evaluating cognitive impairment. While rare diseases such as CJD and HD account for a small proportion of dementia cases, their diagnostic and prognostic implications are substantial. Conversely, disorders such as NPH, HIV-associated dementia, and several toxin- or infection-related conditions may be partially reversible, emphasizing the value of early recognition and targeted intervention.

Collectively, these conditions illustrate the need for a comprehensive diagnostic approach that incorporates clinical assessment, neuroimaging, laboratory testing, genetic evaluation, and consideration of potentially treatable causes of cognitive decline.

Genetic Factors and Pathophysiology

The dementias reviewed in this article arise through diverse biological mechanisms, ranging from inherited genetic mutations and protein misfolding disorders to chronic infection, neuroinflammation, toxic injury, and disturbances in cerebrospinal fluid (CSF) dynamics. Despite these differences, many ultimately converge on common pathways involving synaptic dysfunction, neuronal loss, network disconnection, and progressive cognitive impairment.

Genetic Factors
Genetic contributions vary substantially among these disorders. Huntington's disease (HD) is the clearest example of a monogenic dementia syndrome and results from expansion of a CAG trinucleotide repeat within the huntingtin (HTT) gene. Repeat length correlates inversely with age at onset and influences disease progression, making HD one of the best-characterized neurogenetic disorders (McColgan & Tabrizi, 2018).

Genetic factors also contribute to prion diseases. Approximately 10–15% of Creutzfeldt–Jakob disease (CJD) cases are associated with pathogenic mutations in the prion protein gene (PRNP). In addition, polymorphisms at codon 129 of PRNP influence disease susceptibility and phenotype (Mead, 2022).

In contrast, normal pressure hydrocephalus (NPH), HIV-associated dementia (HAD), and most toxin- or infection-related dementias are not primarily inherited disorders. Nevertheless, genetic variability may influence susceptibility to neurodegeneration, inflammatory responses, and treatment outcomes.

Table 3. Major Genetic Factors in Other Dementias

Disorder	Principal Genetic Factor	Clinical Significance
Huntington's disease	*HTT* CAG repeat expansion	Direct disease cause
Genetic prion diseases	*PRNP* mutations	Familial disease forms
Sporadic CJD	Codon 129 polymorphism	Modifies susceptibility and phenotype
NPH	No established causative gene	Limited genetic contribution
HIV-associated dementia	Host genetic modifiers	Variable susceptibility
Toxic/infectious dementias	No specific causative genes	Environmental predominance

Pathophysiology

Cerebrospinal Fluid Dysfunction in NPH
The pathophysiology of NPH is characterized by impaired CSF circulation and reduced clearance of interstitial metabolites. Progressive ventricular enlargement exerts mechanical stress on periventricular white matter tracts involved in gait, cognition, and bladder control. Emerging evidence also implicates dysfunction of the glymphatic system and age-related vascular changes in disease development (Nakajima et al., 2021).

Protein Misfolding in CJD
CJD represents the prototypical protein misfolding disorder. Conversion of normal cellular prion protein (PrP^C) into a pathological isoform PrP^Sc) initiates a self-propagating cascade of aggregation, neuronal injury, and spongiform degeneration. Unlike conventional infectious agents, prions lack nucleic acids and propagate through conformational templating (Hermann et al., 2021).

Mutant Huntingtin Toxicity in HD
In HD, expanded polyglutamine tracts within mutant huntingtin protein promote intracellular aggregation and disrupt multiple cellular processes, including transcriptional regulation, axonal transport, mitochondrial function, and proteostasis. Progressive degeneration is particularly prominent within the caudate nucleus and putamen, leading to motor, cognitive, and psychiatric manifestations (McColgan & Tabrizi, 2018).

Neuroinflammation in HIV-Associated Dementia
HIV does not directly infect neurons. Instead, infected macrophages and microglia trigger chronic neuroinflammation, cytokine release, excitotoxicity, and synaptic injury. Persistent CNS viral reservoirs may sustain inflammation even in individuals receiving effective antiretroviral therapy (Nightingale et al., 2023).

Toxic and Infectious Injury
Toxin-related dementias arise through diverse mechanisms, including oxidative stress, mitochondrial dysfunction, hypoxic injury, and disruption of neurotransmitter systems. Similarly, infection-related dementias may result from direct microbial invasion, chronic inflammation, vasculitis, hydrocephalus, demyelination, or secondary neuronal loss.

Shared Mechanisms of Cognitive Decline
Despite their distinct etiologies, several biological pathways are common across these disorders:

- Neuroinflammation
- Synaptic dysfunction
- Oxidative stress
- White matter injury
- Network disconnection
- Progressive neuronal loss

These convergent mechanisms help explain why clinically diverse diseases ultimately produce similar cognitive and functional impairments.

Table 4: Comparative Pathophysiological Mechanisms

Disorder	Dominant Mechanism
NPH	CSF circulation and glymphatic dysfunction
CJD	Prion protein misfolding
HD	Mutant huntingtin toxicity
HIV-associated dementia	Chronic neuroinflammation
Toxic dementias	Neurotoxic injury
Infectious dementias	Infection-induced CNS damage

Key Points

Genetic factors are central to Huntington's disease and inherited prion disorders but play a more limited role in NPH, HIV-associated dementia, and most toxin- or infection-related dementias. The underlying pathophysiological mechanisms differ substantially; however, all ultimately lead to neuronal dysfunction and cognitive decline through convergent pathways involving inflammation, cellular injury, and network disruption. Understanding these mechanisms has become increasingly important as biomarker-guided diagnostics and targeted therapies continue to evolve.

Clinical Presentation and Variants

The clinical manifestations of these dementias reflect the underlying anatomical and pathological processes involved. Although cognitive impairment is a shared feature, the pattern of deficits, associated neurological findings, rate of progression, and systemic manifestations often provide important diagnostic clues. Recognition of characteristic clinical syndromes remains essential for early diagnosis and appropriate management.

Clinical Presentation

Normal pressure hydrocephalus (NPH) classically presents with the triad of gait disturbance, cognitive impairment, and urinary dysfunction. Gait impairment is usually the earliest and most prominent feature, often described as a broad-based, slow, "magnetic" gait. Cognitive deficits primarily involve attention, executive function, and psychomotor speed rather than the episodic memory impairment typical of Alzheimer's disease (Nakajima et al., 2021).

Creutzfeldt–Jakob disease (CJD) typically presents as a rapidly progressive dementia developing over weeks to months. Cognitive decline is accompanied by neurological manifestations including myoclonus, cerebellar dysfunction, visual disturbances, pyramidal signs, extrapyramidal symptoms, and eventually akinetic mutism. The unusually rapid progression remains one of the most important diagnostic clues (Hermann et al., 2021).

Huntington's disease (HD) is characterized by a triad of motor, cognitive, and psychiatric symptoms. Chorea is the most recognizable motor feature, although dystonia, bradykinesia, and gait abnormalities may also occur. Cognitive impairment predominantly affects executive function, processing speed, and attention. Depression, irritability, anxiety, apathy, and behavioural dysregulation are common and may precede motor manifestations (McColgan & Tabrizi, 2018).

HIV-associated dementia (HAD) usually presents with a subcortical pattern of impairment characterized by psychomotor slowing, executive dysfunction, impaired attention, and reduced information-processing speed. Behavioural symptoms may include apathy, social withdrawal, and mood disturbance. Motor slowing and gait instability may develop in advanced disease (Nightingale et al., 2023).

Toxin- and infection-related dementias demonstrate considerable clinical variability depending upon the underlying cause. Common manifestations include memory impairment, executive dysfunction, personality change, gait abnormalities, psychiatric symptoms, and fluctuating cognition. Associated systemic features may provide important diagnostic clues.

Major Clinical Features

Table 5. Comparative Clinical Presentation of Other Dementias

Feature	NPH	CJD	HD	HIV Dementia	Toxic/ Infectious
Cognitive Decline	Gradual	Rapid	Progressive	Variable	Variable
Executive Dysfunction	Common	Common	Common	Common	Common
Memory Impairment	Mild–Moderate	Common	Moderate	Mild–Moderate	Variable
Gait Disturbance	Early hallmark	Common	Common	Possible	Variable
Urinary Symptoms	Common	Rare	Rare	Rare	Variable
Myoclonus	Rare	Characteristic	Rare	Rare	Rare
Chorea	Absent	Rare	Characteristic	Absent	Absent
Psychiatric Symptoms	Mild	Possible	Very common	Common	Common
Progression	Months–Years	Weeks–Months	Years–Decades	Variable	Variable

Clinical Variants

Normal Pressure Hydrocephalus
NPH is generally categorized into:
- Idiopathic NPH
- Secondary NPH

Secondary forms occur following conditions such as subarachnoid hemorrhage, meningitis, traumatic brain injury, or neurosurgical procedures. Clinical manifestations are often similar, although secondary NPH may occur at a younger age and have a more clearly identifiable precipitating event.

Creutzfeldt–Jakob Disease
Several clinicopathological variants of CJD have been described. Sporadic CJD is the most common form, whereas genetic, iatrogenic, and variant CJD are less frequent. Certain phenotypic variants may initially present with visual symptoms, cerebellar dysfunction, or psychiatric manifestations, potentially delaying diagnosis.

Huntington's Disease
Adult-onset HD is the most common phenotype. Juvenile Huntington's disease, typically associated with very large CAG repeat expansions, often presents with rigidity, bradykinesia, seizures, and cognitive decline rather than prominent chorea. This variant generally follows a more aggressive clinical course.

HIV-Associated Neurocognitive Disorders
Current classification recognizes a spectrum of disease severity:
- Asymptomatic Neurocognitive Impairment (ANI)
- Mild Neurocognitive Disorder (MND)
- HIV-Associated Dementia (HAD)

This framework reflects the shift from severe dementia toward milder forms of cognitive impairment in the era of effective antiretroviral therapy.

Infection-Related Variants
Clinical phenotypes vary according to the causative pathogen. Neurosyphilis may present with personality change and cognitive decline, tuberculosis may be associated with hydrocephalus and focal deficits, while progressive multifocal leukoencephalopathy often produces cognitive impairment accompanied by focal neurological abnormalities.

Red Flags Suggesting Specific Diagnoses
Certain clinical features strongly favour particular diagnoses:

Table 6. Diagnostic Clinical Red Flags

Clinical Feature	Diagnostic Consideration
Rapid decline over weeks	CJD
Magnetic gait with ventriculomegaly	NPH
Chorea with family history	HD
HIV infection with psychomotor slowing	HAND/HAD
History of toxin exposure	Toxic dementia
Cognitive decline with CNS infection	Infection-related dementia

Clinical Implications
Careful characterization of symptom onset, progression, associated neurological findings, family history, infectious risk factors, and exposure history remains critical in the evaluation of dementia. While substantial overlap exists among syndromes, characteristic clinical patterns frequently provide the first indication of the underlying diagnosis and guide subsequent laboratory, imaging, and genetic investigations.

Diagnosis

Accurate diagnosis of uncommon dementias requires integration of clinical assessment, laboratory testing, neuroimaging, biomarker analysis, and, in selected cases, genetic evaluation. Because several of these disorders are potentially treatable or have important prognostic implications, early identification is essential. The diagnostic approach should focus on distinguishing reversible causes from irreversible neurodegenerative conditions while simultaneously identifying disease-specific features.

Differential Diagnosis
The differential diagnosis varies according to symptom profile and disease tempo. Rapidly progressive cognitive decline raises concern for prion disease, autoimmune encephalitis, central nervous system infection, metabolic disorders, or toxic exposure. In contrast, slowly progressive syndromes are more consistent with NPH, HD, or chronic HIV-associated neurocognitive impairment.

Several clinical features can assist differentiation:
- Early gait dysfunction and urinary symptoms suggest NPH.
- Rapid progression with myoclonus favours CJD.
- Chorea and positive family history strongly suggest HD.
- Psychomotor slowing in an individual with HIV infection supports HAND.
- Exposure history may indicate toxic etiologies.
- Fever, meningismus, or immunosuppression should prompt investigation for infectious causes.

Because symptom overlap is common, clinical evaluation alone is rarely sufficient.

Diagnostic Approach
A structured diagnostic framework is recommended.

Clinical Assessment
The evaluation should include:
- Detailed history of symptom onset and progression
- Functional assessment
- Medication review
- Exposure history
- Family history
- Neurological examination

Special attention should be given to gait abnormalities, movement disorders, psychiatric symptoms, and focal neurological deficits.

Cognitive Assessment
Commonly used instruments include:
- Mini-Mental State Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)
- Addenbrooke's Cognitive Examination III (ACE-III)
- Frontal Assessment Battery (FAB)

The pattern of deficits may provide diagnostic clues. Executive dysfunction is particularly prominent in NPH, HD, and HIV-associated dementia, whereas rapidly progressive global impairment is more characteristic of CJD.

Laboratory Evaluation
Routine laboratory studies remain essential to exclude reversible causes of cognitive decline.

Recommended investigations include:
- Complete blood count
- Electrolytes
- Renal and liver function tests
- Thyroid function tests
- Vitamin B12 and folate levels
- Inflammatory markers
- Syphilis serology
- HIV testing when indicated

Additional investigations should be guided by clinical suspicion.

Disease-Specific Testing
For suspected infectious etiologies:
- Cerebrospinal fluid (CSF) analysis
- Microbiological studies
- Molecular pathogen detection

For suspected toxic disorders:
- Heavy metal screening
- Toxicology testing
- Occupational exposure assessment

For suspected HD:
- HTT genetic testing

For suspected prion disease:
- RT-QuIC testing
- CSF tau
- CSF 14-3-3 protein

(Hermann et al., 2021).

Neuroimaging
Neuroimaging is a central component of diagnosis and frequently provides disease-specific findings.

Magnetic Resonance Imaging
MRI is generally the preferred imaging modality because of its superior sensitivity and anatomical detail.

Characteristic findings include:

Normal Pressure Hydrocephalus
- Ventriculomegaly
- Disproportionately enlarged subarachnoid-space hydrocephalus (DESH)
- Narrow high-convexity sulci
- Reduced callosal angle

(Nakajima et al., 2021).

Creutzfeldt–Jakob Disease
- Cortical ribboning on diffusion-weighted imaging
- Basal ganglia hyperintensity
- Thalamic involvement in selected variants

Huntington's Disease
- Caudate nucleus atrophy
- Striatal volume loss
- Progressive cortical atrophy in advanced disease

HIV-Associated Dementia
- White matter abnormalities
- Cerebral atrophy
- Subcortical changes

Infection-Related Disorders
Findings vary according to pathogen but may include:
- Meningeal enhancement
- Hydrocephalus
- Focal lesions
- Demyelination

Electroencephalography
EEG has limited utility in most dementias but remains valuable in suspected CJD.

Characteristic findings include:
- Periodic sharp-wave complexes
- Diffuse slowing

Although not specific, these findings can support the diagnosis when interpreted alongside clinical and biomarker data.

Biomarkers
Biomarkers have transformed the diagnosis of several neurological disorders and are increasingly incorporated into routine clinical practice.

Cerebrospinal Fluid Biomarkers
Prion Disease
Important markers include:
- RT-QuIC
- Total tau
- 14-3-3 protein

RT-QuIC currently represents the most specific biomarker for CJD and has significantly improved diagnostic accuracy (Hermann et al., 2021).

HIV-Associated Dementia
Potential biomarkers include:
- HIV RNA levels
- Inflammatory mediators
- Neurofilament light chain (NfL)

Although primarily research tools, these markers may assist disease monitoring.

Blood-Based Biomarkers
Growing interest exists in blood biomarkers because they are less invasive and more practical for longitudinal monitoring.

Among the most promising is neurofilament light chain (NfL), which reflects axonal injury and may correlate with disease activity across multiple neurological disorders (Bridel et al., 2019).

Comparative Diagnostic Features

Table 7. Key Diagnostic Findings in Other Dementias

Disorder	Characteristic Diagnostic Features
NPH	Ventriculomegaly, DESH pattern, positive CSF tap test
CJD	Rapid progression, RT-QuIC positivity, cortical ribboning
HD	HTT mutation, caudate atrophy, chorea
HIV Dementia	HIV infection, executive dysfunction, white matter changes
Toxic Dementias	Exposure history, toxicological evidence
Infection-Related Dementias	Microbiological confirmation, inflammatory findings

Diagnostic Strategy
A practical approach begins with clinical assessment and cognitive testing, followed by targeted laboratory investigations and MRI. Genetic testing is reserved for suspected hereditary disorders, while advanced biomarker studies are most useful in prion disease and selected research settings.

Importantly, clinicians should actively search for potentially reversible causes, particularly NPH, HIV-associated cognitive disorders, toxin exposure, and treatable CNS infections. Early diagnosis not only improves management options but may significantly alter long-term outcomes and quality of life.

Management, Prognosis, and Future Directions

Management strategies for other dementias vary considerably because the underlying mechanisms range from potentially reversible disturbances of cerebrospinal fluid dynamics to irreversible neurodegenerative and prion disorders. Nevertheless, several common principles apply across conditions, including early diagnosis, multidisciplinary care, symptom management, rehabilitation, caregiver support, and optimization of quality of life.

Management

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus represents one of the few potentially reversible causes of dementia. The primary treatment is cerebrospinal fluid diversion, most commonly through ventriculoperitoneal shunt placement (Nakajima et al., 2021).

Appropriate patient selection is critical and is generally based on:

- Compatible clinical presentation
- Characteristic neuroimaging findings
- Positive response to CSF drainage testing

Gait dysfunction demonstrates the greatest likelihood of improvement following surgery, whereas cognitive and urinary symptoms often show more variable responses. Postoperative rehabilitation may further enhance functional outcomes.

Creutzfeldt–Jakob Disease

No curative therapy currently exists for CJD. Management is therefore primarily supportive and focuses on symptom control, patient comfort, and palliative care (Mead, 2022).

Common interventions include:

- Treatment of myoclonus with clonazepam or valproate
- Nutritional support
- Prevention of complications related to immobility
- Management of behavioural symptoms
- Advance care planning

Because disease progression is usually rapid, early discussions regarding goals of care are particularly important.

Huntington's Disease

Management of HD requires a multidisciplinary approach involving neurology, psychiatry, rehabilitation medicine, nutrition, and social services.

Pharmacological therapy focuses on symptom control:

Motor Symptoms

- Tetrabenazine
- Deutetrabenazine
- Selected antipsychotic agents

Psychiatric Symptoms

- Antidepressants
- Antipsychotics
- Mood stabilizers

Rehabilitation interventions including physical, occupational, and speech therapy play an important role throughout the disease course (Saft et al., 2023).

HIV-Associated Dementia

The cornerstone of treatment is effective antiretroviral therapy (ART). Viral suppression has dramatically reduced the incidence of severe HIV-associated dementia and remains the most effective intervention for preserving cognitive function (Nightingale et al., 2023).

Additional management strategies include:

- Optimization of ART adherence
- Treatment of psychiatric comorbidities
- Cognitive rehabilitation
- Management of cardiovascular risk factors

Toxin- and Infection-Related Dementias
Treatment depends upon the underlying etiology.

Toxin-Related Disorders
Management may include:
- Removal of toxic exposure
- Alcohol abstinence
- Nutritional supplementation
- Chelation therapy when indicated
- Treatment of complications

Infection-Related Disorders
Therapy is directed toward the causative pathogen and may involve:
- Antibiotics
- Antifungal agents
- Antiviral therapies
- Management of hydrocephalus and other neurological complications

Because many infectious and toxic causes are potentially reversible, early intervention is crucial.

Comparative Treatment Overview

Table 8. Principal Management Strategies

Disorder	Primary Treatment
NPH	Ventriculoperitoneal shunting
CJD	Supportive and palliative care
HD	Symptomatic pharmacotherapy and rehabilitation
HIV Dementia	Antiretroviral therapy
Toxic Dementias	Exposure removal and supportive treatment
Infection-Related Dementias	Pathogen-specific antimicrobial therapy

Prognosis
Prognosis varies substantially among these disorders and depends on disease mechanism, stage at diagnosis, treatment availability, and patient-specific factors.

Normal Pressure Hydrocephalus
Among the conditions reviewed, NPH offers one of the most favourable prognostic profiles because meaningful improvement may occur following shunt surgery. Early diagnosis, shorter symptom duration, and positive CSF drainage testing are associated with better outcomes (Nakajima et al., 2021).

Creutzfeldt–Jakob Disease
CJD carries the poorest prognosis. Median survival is generally measured in months, and most patients experience relentless neurological deterioration despite supportive care (Hermann et al., 2021).

Huntington's Disease
HD follows a chronic progressive course. Survival typically ranges from 15 to 25 years following symptom onset, although considerable variability exists. Disease progression is influenced by CAG repeat length, age at onset, and comorbidity burden (McColgan & Tabrizi, 2018).

HIV-Associated Dementia
The prognosis of HIV-associated dementia has improved dramatically in the era of combination ART. Many patients achieve stabilization or partial improvement, although residual cognitive deficits frequently persist (Nightingale et al., 2023).

Toxic and Infectious Dementias
Outcomes depend largely on the speed of diagnosis and treatment. Early intervention may result in substantial recovery, whereas delayed recognition can lead to permanent neurological injury.

Table 9. Comparative Prognosis

Disorder	Typical Clinical Course	Potential Reversibility
NPH	Often improved with treatment	Moderate–High
CJD	Rapidly progressive and fatal	None
HD	Slowly progressive	None
HIV Dementia	Variable, improved with ART	Partial
Toxic Dementias	Variable	Variable
Infection-Related Dementias	Variable	Often significant

Future directions

Recent advances in neuroscience, genetics, biomarker development, and computational medicine are reshaping the diagnosis and management of dementia.

Biomarker Development
Blood-based biomarkers such as neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) may facilitate earlier diagnosis, disease monitoring, and prognostic assessment (Hansson, 2024).

Precision Medicine
Precision medicine approaches aim to integrate:
- Genetic information
- Biomarker profiles
- Neuroimaging findings
- Clinical phenotypes

to guide individualized treatment strategies.

Gene-Targeted Therapies
HD has emerged as a leading target for gene-based interventions, including:
- Antisense oligonucleotides
- RNA-targeted therapies
- Gene-silencing approaches

Although still investigational, these strategies represent one of the most promising developments in neurodegenerative disease research (Tabrizi et al., 2024).

Artificial Intelligence
Artificial intelligence and machine-learning technologies may improve:
- Neuroimaging interpretation
- Diagnostic accuracy
- Prognostic prediction
- Clinical decision support

These tools are increasingly being incorporated into dementia research and clinical practice.

Prevention
Future public health strategies should emphasize:
- HIV prevention and treatment
- Occupational safety
- Environmental toxin reduction
- Infection control
- Early identification of treatable neurological disorders

Prevention remains particularly important because several causes of cognitive decline discussed in this review are potentially avoidable or reversible.

Conclusion

Other dementias comprise a diverse group of neurological disorders that differ markedly in etiology, pathophysiology, clinical presentation, treatment options, and prognosis. Normal pressure hydrocephalus, Creutzfeldt–Jakob disease, Huntington's disease, HIV-associated dementia, and toxin- and infection-related dementias illustrate the broad range of mechanisms capable of producing cognitive impairment.

Recognition of these disorders is clinically important because several are potentially treatable and require disease-specific management. Advances in neuroimaging, molecular diagnostics, biomarkers, genetics, and precision medicine are improving diagnostic accuracy and expanding therapeutic possibilities. Continued research into disease mechanisms and targeted interventions offers the prospect of earlier diagnosis, improved outcomes, and more individualized care for patients affected by these challenging conditions.

Table 10. Key Clinical Messages

Key Message	Clinical Importance
NPH remains one of the most treatable causes of dementia	Early recognition can improve outcomes
CJD should be considered in rapidly progressive dementia	Prompt diagnosis facilitates appropriate management
HD requires genetic confirmation and multidisciplinary care	Essential for patient and family counseling
HIV-associated cognitive disorders remain clinically relevant	ART optimization improves outcomes
Toxic and infectious causes must always be excluded	Many are reversible if detected early
Biomarkers and precision medicine are transforming dementia care	Likely to influence future clinical practice

References

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., Clifford, D. B., Cinque, P., Epstein, L. G., Goodkin, K., et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. Neurology, 69(18), 1789–1799. https://doi.org/10.1212/01.WNL.0000287431.88658.8b

Bridel, C., van Wieringen, W. N., Zetterberg, H., Tijms, B. M., Teunissen, C. E., Alvarez-Cermeño, J. C., Andreasson, U., Axelsson, M., Bäckström, D. C., Bartos, A., et al. (2019). Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: A systematic review and meta-analysis. JAMA Neurology, 76(9), 1035–1048. https://doi.org/10.1001/jamaneurol.2019.1534

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. New England Journal of Medicine, 372(9), 793–795. https://doi.org/10.1056/NEJMp1500523

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: A frontal assessment battery at bedside. Neurology, 55(11), 1621–1626.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12(3), 189–198.

Hansson, O. (2024). Biomarkers for neurodegenerative diseases. Nature Medicine, 30(1), 18–29.

Hermann, P., Appleby, B., Brandel, J. P., Caughey, B., Collins, S., Geschwind, M., Green, A., Haïk, S., Kovacs, G. G., Ladogana, A., et al. (2021). Biomarkers and diagnostic guidelines for Creutzfeldt–Jakob disease. The Lancet Neurology, 20(3), 235–246.

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 36(3–4), 242–250.

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., et al. (2024). Revised biological framework for neurodegenerative disease diagnosis and biomarker classification. Alzheimer's & Dementia, 20(1), 1–28.

Kovacs, G. G. (2023). Neuropathology of neurodegenerative diseases (2nd ed.). Cambridge University Press.

McColgan, P., & Tabrizi, S. J. (2018). Huntington's disease: A clinical review. European Journal of Neurology, 25(1), 24–34.

Mead, S. (2022). Prion disease therapeutics: Progress and challenges. Nature Reviews Neurology, 18(6), 353–367.

Nakajima, M., Yamada, S., Miyajima, M., Kazui, H., Mori, E., Ishikawa, M., & Guideline Committee for Idiopathic Normal Pressure Hydrocephalus. (2021). Guidelines for management of idiopathic normal pressure hydrocephalus (3rd ed.). Neurologia Medico-Chirurgica, 61(2), 63–97.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment (MoCA): A brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society, 53(4), 695–699.
Nightingale, S., Winston, A., Letendre, S., Michael, B. D., McArthur, J. C., Khoo, S., Solomon, T., & Robertson, K. (2023). HIV-associated neurocognitive disorders in the modern antiretroviral era. The Lancet Neurology, 22(5), 431–446.
Olmedo-Saura, M., Tabrizi, S. J., & Wild, E. J. (2025). Emerging therapeutics for Huntington's disease. Nature Reviews Drug Discovery, 24(2), 112–130.
Petersen, R. C., Lopez, O., Armstrong, M. J., Getchius, T. S. D., Ganguli, M., Gloss, D., Gronseth, G., Marson, D., Pringsheim, T., Day, G. S., et al. (2024). Practice guideline update summary: Mild cognitive impairment. Neurology, 102(4), e200–e218.
Ropper, A. H., Samuels, M. A., Klein, J. P., & Prasad, S. (2023). Adams and Victor's Principles of Neurology (12th ed.). McGraw-Hill.
Saft, C., Orth, M., & Reilmann, R. (2023). Contemporary pharmacological management of Huntington's disease. Journal of Neurology, 270(9), 4321–4335.
Tabrizi, S. J., Leavitt, B. R., Landwehrmeyer, G. B., Wild, E. J., & McColgan, P. (2024). Gene-targeted therapies in Huntington's disease. The Lancet Neurology, 23(1), 55–71.
World Health Organization. (2023). Global status report on the public health response to dementia. World Health Organization.
Zerr, I., Villar-Piqué, A., Hermann, P., Schmitz, M., & Ladogana, A. (2020). Cerebrospinal fluid and blood biomarkers in prion diseases. Nature Reviews Neurology, 16(9), 539–552.