

Chapter 23

Young-onset dementias

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Key points

- Patients with young-onset dementia, including Down syndrome, require careful evaluation to rule out treatable causes of dementia.
- Biomarkers play a major role ruling out Alzheimer's disease in young-onset dementia.



General background

Young-onset (also referred to as early-onset) refers to people under the age of 65 who are diagnosed with dementia. Although the cut-off at age 65 is arbitrary, it has been established that the cause of dementia can vary greatly among younger people. Determining its underlying cause in a definitive way is critical as it may affect how their condition is managed. Among the several diseases that cause dementia in young people, some are degenerative such as Alzheimer's disease, but others may be related to brain circulation, cancer, infections or

even genetic conditions. Therefore, the diagnosis and management of these individuals should be conducted in tertiary centres staffed with multidisciplinary teams (1–4). Many of these issues are explored more fully in the expert essays contained within this Chapter. They detail some of the complexities unique to this diagnosis and detail the journey taken by young individuals. A thorough medical investigation of these cases is vital as many of them may require specialised therapies to address the underlying cause of their dementia.

Survey results

The survey reveals a consensus of referring young-onset dementia patients to specialised centres (Chart 1). However, results also indicate that 11% of the 1,111 clinicians do not refer to specialised centres. This is largely due to a lack of available specialists or the high cost of these assessments. Approximately 17% of the respondents refer to a specialist at either the patient's or the family's request.

Specifically, regarding patients with previous intellectual disabilities (i.e. neurodevelopmental disorders or genetic conditions) only 21% of respondents refer to a clinician with experience in this specific issue, while 38% refer to a neuropsychologist.

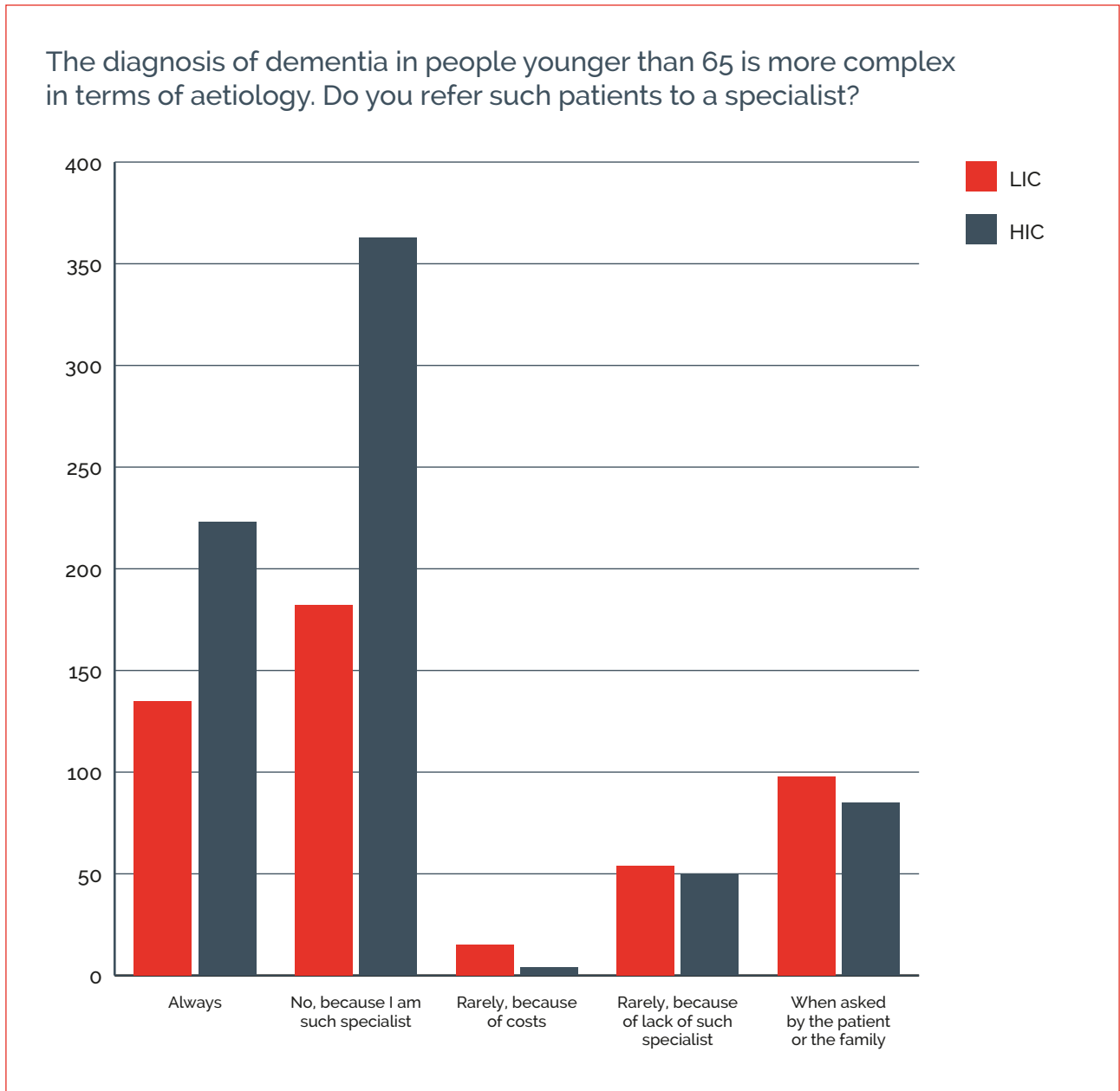


Chart 1. Clinician responses.

Causes of young-onset dementia

Although Alzheimer's disease, frontotemporal and Lewy body dementias account for the symptoms in almost half of young-onset dementia cases, the prevalence of rarer dementia causes (rare vascular causes, infectious, inflammatory, autoimmune, genetic abnormalities or metabolic) increases in individuals under the age of 65. As many of these causes are treatable, the first assessment by a general practitioner should be followed up by a referral to either a memory centre or general neurology for further clinical investigation. Rare disorders are frequently associated with neurologic and systemic manifestations (Table 1). A summary of the causes of dementia in young people is illustrated in the section below (2.5–7).

The cause of dementia presents as even more atypical for those individuals younger than 35 years of age.

Alzheimer's disease – Certain clinical scenarios are associated with young-onset Alzheimer's disease. The APOE4 genotype is a common generic risk factor associated with

Alzheimer's dementia symptoms before the age of 65. Down syndrome is another frequent genetically-driven cause of Alzheimer's disease seen in the third and fourth decades of life. Carriers of autosomal dominant Alzheimer's disease may present dementia symptoms as early as in their third decade; however, these families are rare. Sporadic Alzheimer's disease may resemble the amnesic typical clinical presentation of specific dementias. As well, nearly 10% of these individuals may have de novo mutations in PS1, PS2 and APP genes.

These non-amnesic atypical variants of Alzheimer's disease have only been fully incorporated in the operational definition of Alzheimer's disease in 2010–2011. Recent biomarker research has also shown that tau pathology and neurodegeneration rather than amyloid pathology correlate with Alzheimer's dementia symptoms (Figure 1). These patterns of tau distribution observed in the PET scans constitute signatures of these specific Alzheimer's disease subtypes (8–11).

Table 1. Systemic and neurological abnormalities associated with young-onset dementias

Neurological or systemic abnormalities	Rare causes for early-onset dementias
Abnormal gait and station	Normal pressure hydrocephalus, Parkinson's dementia, progressive supranuclear palsy, vascular dementia, neurosyphilis, Type 1 myotonic dystrophy, autosomal dominant Alzheimer's disease (spastic paraparesis), chronic traumatic encephalopathy
Anaemia	Vitamin B12 deficiency, neuroacanthocytosis, Wilson disease, alcohol abuse
Ataxia	Spinocerebellar atrophy, paraneoplastic encephalopathy, prion disease, dentatorubral-pallidoluysian atrophy, multiple system atrophy, leukoencephalopathies, mitochondrial diseases
Cardiac disease	Late-onset Fabry disease, Type 1/2 myotonic dystrophy, Down Syndrome
Gastrointestinal dysfunction	Whipple disease
Liver dysfunction	Wilson disease, Gaucher disease, mitochondrial diseases
Migraine and stroke	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, mitochondrial diseases, chronic traumatic encephalopathy
Paget disease of bone	Frontotemporal dementias
Renal impairment	Late-onset Fabry disease, mitochondrial disease
Respiratory disease	Frontotemporal with motor neuron diseases, mitochondrial disease, anti-NMDAR encephalitis, Type 1 myotonic dystrophy
Skin lesions	Systemic vasculitis, late-onset Fabry disease
Sleep disturbance	Neurodegenerative dementias, prion disease
Splenomegaly	Niemann-Pick type C, Gaucher disease
Tendon xanthomas	Cerebrotendinous xanthomatosis
Urinary incontinence	Normal pressure hydrocephalus

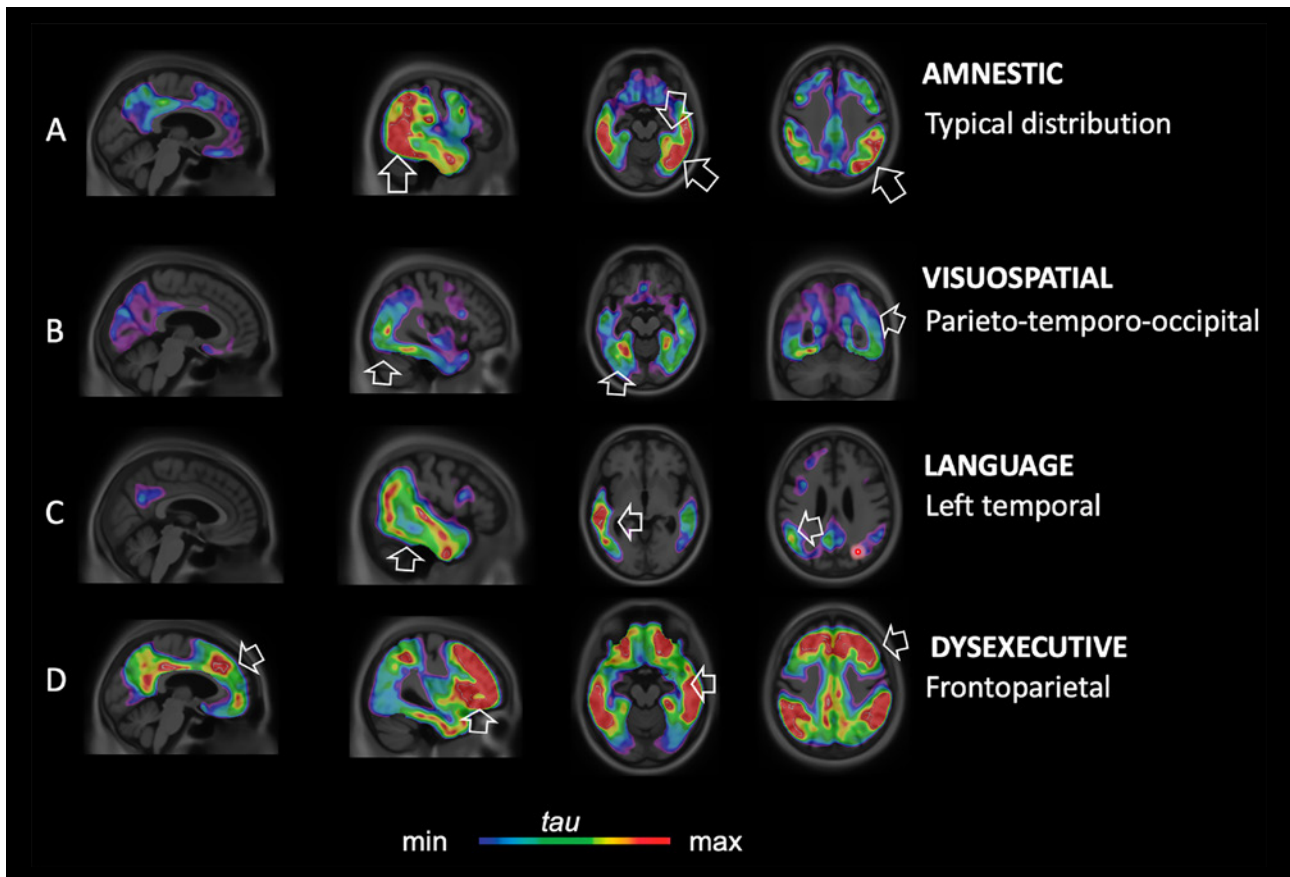


Figure 1. These images represent the distribution of neurofibrillary tangles (rainbow colour) overlaid in a structural MRI (grey tone). The amnesic type of Alzheimer's disease (A) shows tau deposition in the trans and entorhinal areas, limbic cortices, associative neocortex and in the most advanced cases in the primary sensory areas. Note that in visuospatial (B), language (C) and dysexecutive variants of Alzheimer's disease (D) neurofibrillary tangles accumulate in the parieto-temporo-occipital, left temporoparietal and frontoparietal regions, respectively (12, 13).

Other degenerative causes of young-onset dementia

Frontotemporal dementia – A behavioural variant, semantic dementia and progressive non-fluent aphasia are inescapable clinical manifestations of frontal and temporal lobes degeneration. While the behavioural variant features a progressive decline in social cognition and executive function, the semantic and non-fluent primary progressive aphasias are characterised by a degeneration that affects both language centres responsible for semantic and phoneme production (14).

Lewy body dementias – Young-onset Lewy body dementias, including Parkinson's disease dementia and dementia with Lewy bodies, may be associated with alpha-synuclein gene copy number variations, glucocerebrosidase gamma-synuclein gene mutations (15).

A wide range of disease processes underlie **vascular dementia** in young individuals. Inherited vascular dementias causes microangiopathy, lacunar infarcts predominantly

in the anterior quadrant of the brain and causes frequent migraines, neuropsychiatric symptoms (such as depression and irritability) and executive dysfunction. This points to dementia onset in the fifth decade of life. Mutations in the NOTCH3 gene on chromosome 19 leads to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Mutations on the CTSA gene lead to cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL).

Individuals with CARASAL may present with migraine, transient ischemic attacks, stroke with central facial palsy, cognitive dysfunction with impaired concentration, dementia, depression, movement disorder, vertigo, dysphagia, dysarthria, sicca syndrome, impaired REM sleep, and therapy-resistant hypertension, among others. Brain MRI typically shows a leukoencephalopathy that is disproportionately severe and extensive compared to the clinical disease (16–18).

Cerebral amyloid angiopathy is characterised by amyloid beta-peptide deposits within the brain's small- to medium-sized blood vessels and meninges. Dementia is a consequence of progressive brain infarcts and lobar haemorrhages induced by amyloid deposits on the blood vessels.

Among the **infectious causes** of young-onset dementia are HIV-associated neurocognitive disorder, neurosyphilis, herpes encephalitis, Whipple's disease, and progressive multifocal leukoencephalopathy.

Primary angiitis of the central nervous system (PACNS) is caused by an elusive immune-mediated attack on small and medium blood vessels resulting in vessel occlusion, thrombosis and tissue ischemia. Secondary angiitis of the central nervous system can be the result of systemic autoimmune vasculitis (namely Behçet syndrome and Lupus), or an infectious process (such as varicella zoster virus, neurosyphilis or Lyme disease). Brain angiitis leads to cognitive dysfunction. In these instances, these may be accompanied by headaches, seizures, stroke, and cerebral haemorrhage (19,20).

Paraneoplastic and autoimmune encephalitis are clinically characterised by rapidly progressive dementia with a fluctuating course and other neurological manifestations such as seizures. They are caused by Anti-Hu (ANNA-1) or anti-leucine-rich glioma inactivated 1 (LGI1) antibodies. Nonparaneoplastic autoimmune encephalopathies can present clinically as a rapidly progressive dementia such as Hashimoto encephalopathy. Slow and progressive cognitive decline has been described in individuals with systemic Lupus erythematosus and Sjögren, and Behçet syndromes. Rare forms of young-onset dementia are summarised in Table 2 (21,22).

Chronic traumatic encephalopathy designates the progressive cognitive decline characterised by executive impairment, associated with behavioural (irritability, personality changes, depression, and suicidality) motor (parkinsonism), speech and gait abnormalities following repeated traumatic brain injuries. These symptoms have

been frequently observed in professional athletes exposed to repetitive head trauma, particularly professional boxers and football players. Members of the army or other professionals exposed to repetitive traumatic brain injuries might suffer from similar symptoms. The brain lesions found in the brain of these patients is neuronal and astrocytic accumulation of hyperphosphorylated tau aggregates. These abnormalities occur on the superficial cortical layers, within the depths of cortical sulci (8–11).

Substance abuse is a cause of dementia in young adults. Alcohol-related syndromes such as Korsakoff syndrome or disease are well-known as causes of dementia. People with Korsakoff syndrome have substantial anterograde memory impairment and confabulation. These symptoms are associated with lesions in the anterior thalamus rather than mammillary bodies. Marchiafava-Bignami relates to the demyelination and necrosis of the corpus callosum, due to alcohol abuse. Neuropathological studies have shown that substantial brain damage resulting from abusing such drugs as methamphetamine, cocaine-crack and heroin may inflict significant cognitive decline (12). Episodic memory and executive function deterioration as well as language abnormalities have been described in these cases.

Pseudodementia or cognitive abnormality imposed by a mental health condition is often confounded with dementia as it manifests with forgetfulness, difficulties in multitasking, excessive inattention, apathy, reduced energy, and distractibility. Depression and anxiety and other psychiatric conditions may potentially cause severe cognitive deficiency, though this may be potentially reversible with the appropriate therapy. Other reversible causes of dementia have been discussed in the Chapter (15,23–26).

The expert essays describe some of the complexities involved in the diagnosis journey of young individuals affected by dementia. The investigation of these patients is crucial as many may require specific therapies for the underlying cause of dementias.

Table 2. Rare genetic causes of young-onset dementia

Diseases	Protein abnormality	Chromosome
Mitochondrial disease	Energy metabolism	Mitochondrial DNA
Hereditary diffuse leukoencephalopathy with axonal spheroids	Colony-stimulating factor 1 receptor (CSF1R)	5
Adult-onset autosomal dominant leukodystrophy	LMNB1 duplication (intermediate filament)	5
Adult polyglucosan body disease	GBE1	3
Adult neuronal ceroid lipofuscinosis (Kufs disease)	DNAJC5	20
Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL)	CTSA gene - β -galactosidase and neuraminidase 1	20
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	NOTCH3 gene on chromosome 19	19
Wilson's disease	Intracellular copper transporter ATP7B	13
Huntington's disease	Mutations in the HTT gene cause Huntington disease	4

Expert essay

What is the most efficient way to diagnose dementia in a young person?

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What is young-onset dementia and how common is it?

Young or early-onset dementia refers to a brain condition of progressive deterioration in cognitive and mental abilities that significantly impairs occupational functioning and daily life in individuals under the age of 65 (1). While it is uncommon compared to late-onset dementia (that is over 65), young-onset dementia is still estimated to account for between 2% and 10% of all dementia cases worldwide and carries with it an enormous health and economic burden for individuals, their families and society overall (2). This is because it primarily affects individuals of working age with young families, leading to lost productivity, psychosocial distress, and significant cost to healthcare systems. Given that certain conditions causing or mimicking young-onset dementia have treatments, even if just for symptoms in some cases, it is important to be able to accurately diagnose young-onset dementia, identify its potential aetiology and counsel the individuals and their families. Furthermore, with the anticipated advent of disease-modifying therapies for neurodegenerative diseases, such as Alzheimer's disease, employing an appropriate diagnostic approach will be key to targeting the 'right' treatments to individuals (precision medicine) in the future (1).

How do you diagnose young-onset dementia?

A good clinical history followed by a thorough general and neurological exam are the necessary first steps to an accurate diagnosis. Using a systematic clinical and investigational approach, the goal is to rule out any potentially treatable conditions and to identify associated clinical features that may provide clues to narrowing down the differential diagnosis. Rossor et al. have coined the term 'dementia-plus' to refer to other neurological (for example, parkinsonism, focal weakness, etc.) or non-neurological features (evidence for involvement of other organ systems, such as skin and/

or joint changes) that may be observed in association with the primary neurocognitive disorder (3). Special attention should also be paid to family history, as well as infectious (such as Human Immunodeficiency Virus [HIV]) and toxin (for example, heavy alcohol use) exposures.

Cognitive screening should be done as part of this initial assessment. Tests such as the Montreal Cognitive Assessment (4) and/or Mini-Mental State Exam (5), among others, should be employed. Important considerations include validation of the cognitive screening test in the population in which it is intended to be used, including language, education, and cultural factors (6). Specific patterns of cognitive impairment identified on testing may assist with the differential diagnosis. For a comprehensive diagnostic algorithm based on cognitive profile and associated clinical features, please refer to Masellis et al. (1).

Basic blood work looking for potentially treatable causes of cognitive impairment (such as anaemia, vitamin B12 or other vitamin deficiencies, thyroid abnormalities) should be screened in everyone. Brain imaging should also be done to rule out structural abnormalities, such as brain tumours, cerebrovascular disease, or infectious cysts (neurocysticercosis; relevant in low-income countries), and to identify neuroanatomical features of the different causes of dementia. Ideally, this should be done with high-resolution structural Magnetic Resonance Imaging (MRI). If this is not available, then a Computer Axial Tomography (CAT) scan should be the minimum standard. If available, functional brain imaging should also be pursued to investigate for regional perfusion (Single Photon Emission Computed Tomography [SPECT]) or metabolic (Positron Emission Tomography [PET]) signatures of the different types of dementia. Electroencephalogram (EEG) is also useful in ruling out epileptic seizures as a cause or a contributing factor to dementia. Cerebrospinal Fluid (CSF) analysis should be done in the majority of people to exclude inflammatory and infectious causes and to further refine the differential diagnosis. If available, tests such as CSF beta-amyloid, total tau,

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and phospho-tau levels can support a diagnosis of Alzheimer's disease (7). Amyloid and Tau PET may also be of use for determining Alzheimer disease's pathology (7), in particular, but costs limit their routine use in most low- and middle-income countries. Dopamine transporter SPECT may also be helpful in select cases in the differential diagnosis of Lewy body disorders (7). Specialised genetic and biochemical testing for young-onset dementia should be considered based on age at onset, family history, associated clinical features, and brain imaging findings.

What are the causes of young-onset dementia?

While neurodegenerative diseases, such as Alzheimer's disease, are still the most prevalent causes even in this age group, reversible or treatable causes are relatively more prevalent in young-onset dementia compared to late-onset cases. Furthermore, rare genetic or metabolic disorders are also more common in early-onset dementia, especially in those under the age of 35 and treatments may also be available for some of these conditions (8). Therefore, determining a specific familial inheritance pattern is of utmost importance towards guiding appropriate specialised investigations. In these cases, it may also be helpful to refer to a clinical geneticist or genetics counsellor for further genetic and/or biochemical testing.

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Neurodegenerative and other aetiologies

Early-onset Alzheimer's disease is the most common neurodegenerative cause of dementia in the young. While sporadic cases, those with no strong genetic component, are predominant in this early-onset age group, familial Alzheimer's disease is still more frequent than in late-onset cases. In familial cases, an autosomal dominant pattern of inheritance is seen with mutations observed in one of three genes: presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) (9). These account for less than 2% of all young-onset Alzheimer's cases (10). While a memory deficit is the most common clinical presentation of both early-onset sporadic and familial Alzheimer's disease in the majority of cases, atypical variants with visuospatial, language, or behavioural/executive problems occur more frequently than in late-onset forms (1).

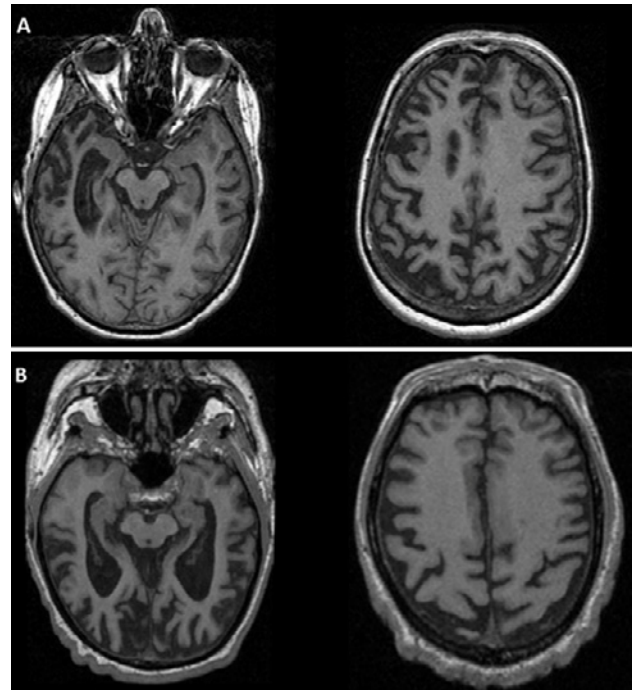


Figure 1. Contrasting atrophy patterns for behavioural variant frontotemporal dementia and early-onset familial Alzheimer's disease. Axial T1 magnetic resonance imaging contrasting atrophy patterns for (a) a patient with behavioural variant frontotemporal dementia due to progranulin (GRN) mutation and (b) a patient with early-onset familial Alzheimer's disease due to presenilin (PSEN1) mutation. (a) Striking asymmetry in frontotemporal and parietal lobes associated with GRN mutations. (b) More symmetrical mesiotemporal and posterior predilection associated with PSEN1 mutations. Reproduced from Masellis M, et al.: Early-onset dementias: diagnostic and etiological considerations. *Alzheimer's Research & Therapy* 2013, 5(Suppl. 1): S7, under the Creative Commons Attribution License (CC BY 4.0, <https://creativecommons.org/licenses/by/4.0/>).

Frontotemporal dementia is the second most common neurodegenerative cause of dementia in this age group with its prevalence approaching that of Alzheimer's disease (11). This heterogeneous group of neurodegenerative disorders presents with either prominent behavioural/executive dysregulation (namely, behavioural variant frontotemporal dementia) or language problems (that is, primary progressive aphasia) early on. Frontotemporal dementia is more strongly genetic than young-onset Alzheimer's disease with autosomal dominant mutations observed in the microtubule associated protein Tau (MAPT) and progranulin (GRN) genes, as well as hexanucleotide repeat expansions in the C9orf72 gene; each genetic subtype accounts for ~5 to 10% of all frontotemporal dementia cases (12). Figure 1 demonstrates the utility of structural MRI in distinguishing genetic Alzheimer's disease from genetic frontotemporal dementia.

Parkinson-Lewy body spectrum disorders represent another related group of conditions that can cause dementia in the young, including Parkinson's disease dementia and dementia with Lewy bodies. People may present with motor symptoms that affect their gait, cause muscle rigidity, tremor, and

slowness (parkinsonism), fluctuations in attention and alertness, visual hallucinations and abnormal behaviours while dreaming (13). While Parkinson-Lewy body disorders are most commonly sporadic, mutations or polymorphisms in certain genes, such as alpha-synuclein (SNCA), glucocerebrosidase (GBA1), and apolipoprotein E (APOE), can cause or increase risk for their occurrence (14). All of these neurodegenerative disorders progress relentlessly, resulting in the need for supportive care of those afflicted in the moderate to severe dementia stages and ultimately culminating in death.

The link between poorly controlled cardiovascular risk factors (including hypertension, diabetes, high cholesterol and smoking) and risk for dementia is well-established (15). While pure forms of vascular cognitive impairment are relatively uncommon, small vessel disease of the brain in conjunction with Alzheimer's disease co-pathology (that is, mixed disease) is the most common form of late-onset dementia. While less prevalent, a cause in young-onset cases, especially in high income countries, stroke and dementia are rising in

low- to middle-income countries making it an important contributor to mixed disease even in young-onset cases (16). Individuals typically present with deficits in executive functions, psychomotor processing speed, and mental flexibility (namely, fronto-subcortical dementia). Since cardiovascular risk factors are modifiable, there is hope that managing them with medications and lifestyle interventions might reduce the incidence of dementia (16). In addition, some rare genetic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) due to NOTCH3 gene mutations, should be considered depending on patient and family history, as well as imaging findings (Figure 2).

Rare genetic and/or metabolic conditions, including lysosomal storage diseases, disorders of amino acid and organic acid metabolism, mitochondrial diseases, leukodystrophies, and disorders of metal metabolism can also cause dementia, most often with other associated clinical features, in the young. These have been reviewed in detail elsewhere (17).

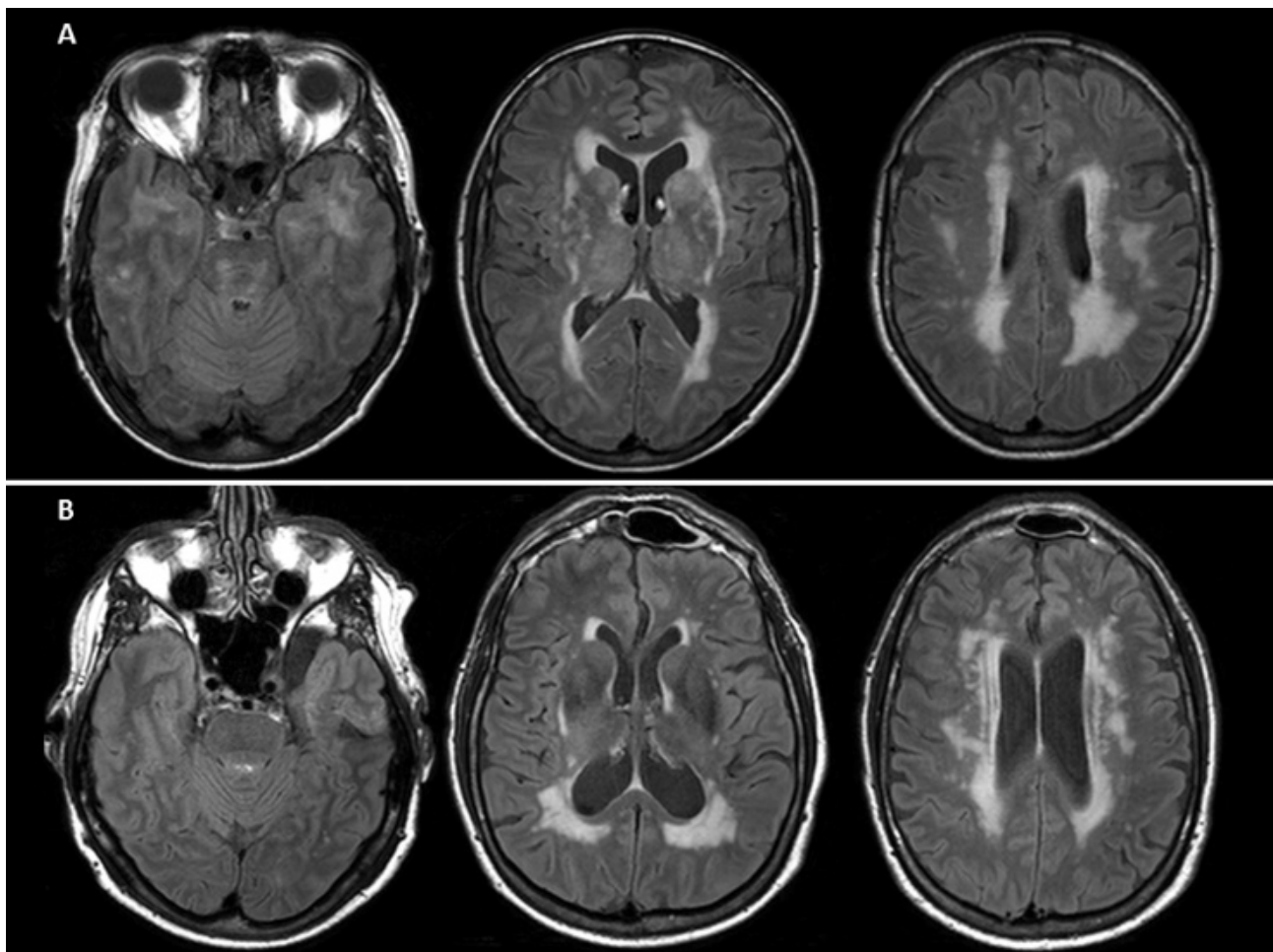


Figure 2. Subcortical ischemic vascular changes in CADASIL and vascular cognitive impairment due to small vessel disease. Axial T2/fluid-attenuated inversion recovery magnetic resonance imaging demonstrating subcortical ischemic vascular changes in (a) a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and (b) a patient with vascular cognitive impairment due to small vessel disease. Anterior temporal lobe involvement distinguishes CADASIL from small vessel disease due to cerebrovascular risk factors. Reproduced from Masellis M, et al. Early-onset dementias: diagnostic and etiological considerations. *Alzheimer's Research & Therapy* 2013, 5(Suppl.1):S7, under the Creative Commons Attribution License (CC BY 4.0, <https://creativecommons.org/licenses/by/4.0/>).

It is important to consider these entities since some, such as Wilson's disease presenting with dementia, parkinsonism and/or psychiatric symptoms, have disease-modifying therapies available.

What should not be missed?

Obstructive sleep apnoea is a common disorder in which recurrent pauses in breathing (apnoeas/hypopnoeas) during sleep cause intermittent hypoxia, hypercapnia and fragmented sleep (18). This condition can be associated with cognitive impairment. One study demonstrated that 8% of people presenting to a young-onset dementia clinic had obstructive sleep apnoea (19). It is potentially treatable via continuous positive airway pressure (CPAP), which might help with cognitive symptoms, in particular inattention.

The autoimmune encephalopathies are a rare group of potentially steroid-responsive syndromes, often affecting young individuals, presenting with subacute onset of cognitive impairment, and frequently accompanied by psychiatric disturbances, confusion, seizures and cortical T2-weighted signal changes on MRI, most often involving the temporal lobe (20). Auto-antibodies targeting several cell-surface brain receptors or ion channels are the cause of inflammatory brain changes involving limbic structures. These antibodies can be assessed in CSF and plasma/serum, which can aid with specific syndromic diagnosis and initiation of immunomodulating therapies.

Temporal lobe epilepsy can be associated with transient epileptic amnesia, which can mimic the memory symptoms of Alzheimer's disease (21). People may present with altered awareness or cognitive fluctuations in addition to anterograde and retrograde amnesia. This condition can be diagnosed via EEG demonstrating temporal lobe spike and wave activity, and brain MRI showing mesiotemporal sclerosis. There may

be some improvement with anticonvulsant therapy, although complete symptom resolution does not always occur.

Special considerations for low- and middle-income countries about treatable causes

While neurodegenerative causes of young-onset dementia are prevalent in low- and middle-income countries, in addition to a higher burden of vascular cognitive impairment as previously mentioned, communicable diseases are an important contributor to cognitive dysfunction due to their higher prevalence. HIV-associated neurocognitive disorder and neurocysticercosis, among others, are potentially treatable causes of cognitive impairment and should be considered on the differential diagnosis of young-onset dementia in these geographical regions (22). The endemic nature of a particular infection should be determined when ordering specific microbiological diagnostic tests.

In summary, young-onset dementia poses unique challenges for afflicted individuals, their families, healthcare systems and society on the whole. A rational diagnostic approach is necessary to first ensure that treatable contributing factors or causes of dementia are excluded, and then to determine the specific neurodegenerative, hereditary or genetic metabolic aetiologies. Access to genetic counselling and other specialised care services should be provided by healthcare systems. Treatment or reduction of 12 potentially modifiable risk factors for late-onset dementia (namely head injury, excess alcohol consumption, air pollution, lower education, hypertension, smoking, diabetes, obesity, physical inactivity, depression, social isolation, and hearing impairment) may prevent dementia or delay its onset (23), especially for younger individuals with risk factors and lacking a strong family history suggestive of a genetic disorder.

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Expert essay

Particular challenges for diagnosing Alzheimer's disease in young people under 65

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Clinical presentation

Aside from the typical amnesic presentation, individuals with young-onset Alzheimer's disease have, more often than those with late-onset Alzheimer's disease, an atypical non-amnesic syndrome with executive, language, or visuo-spatial dysfunction (1). Among the atypical clinical presentations, the most frequent is the biparietal syndrome characterised by a visuospatial deficit, apraxia, agraphia, logopenic aphasia and deficit of auditory-verbal short-term memory. The other most frequent atypical presentation of young-onset Alzheimer's disease is logopenic variant primary progressive aphasia (LPA), posterior cortical atrophy (PCA) or Benson's syndrome and the behavioural/dysexecutive variant. In LPA, language deficit is the initial symptom, characterised by repeated pauses that disrupt the flow of the conversation and the generation of phonologic errors, associated with deficit in sentence repetition. In PCA, visuospatial deficit is the initial symptom, and individuals then develop features of Balint syndrome (ocular apraxia, optic ataxia, and simultanagnosia), Gerstmann syndrome (acalculia, agraphia, finger agnosia, and left-right disorientation), visual agnosia, and transcortical sensory aphasia, whereas episodic memory is preserved or only mildly impaired. The behavioural/dysexecutive variant of Alzheimer's disease is defined by a predominant dysexecutive syndrome which is frequently associated with frontal behavioural symptoms (1). These clinical features can lead to a misdiagnosis of behavioural variant frontotemporal dementia. In young-onset Alzheimer's disease, the initial complaint is not always purely cognitive. In a recent study, 32% of young people with a diagnosis of Alzheimer's disease had an atypical complaint, leading to an initial diagnosis of a burnout syndrome. Among those with young-onset Alzheimer's disease who had a professional activity (70%), a burnout-like syndrome was the first diagnosis in almost half of the cases (2). These people had an inability to carry out concurrent professional tasks, leading to a reduction of professional efficacy and severe anxiety, in the absence of overt language, memory, gestural, visuo-spatial disorders, or other neurological signs. Their family members did not report any specific cognitive

abnormality. Because of these atypical clinical presentations, an Alzheimer's disease diagnosis is not always the first to be ascribed to such young individuals and young-onset Alzheimer's disease cases are often referred to other specialists before neurologists. Instead, should they receive an initial diagnosis of burnout, they are usually referred to psychiatrists and followed for several years before the first neurological evaluation. Also, it is common for patients with PCA to be referred to several ophthalmologists before the first neurological evaluation. The diagnosis of young-onset Alzheimer's disease is delayed by about a 1.6-years average compared to people with late-onset Alzheimer's disease (3), due in part to these atypical clinical presentations and not to anosognosia, which is less pronounced in young individuals. The rapidity of clinical decline is also one of the main elements differentiating young- and late-onset. Several studies indicate that these early-onset patients have a more aggressive disease course (4).

Structural brain and fluorodeoxyglucose-positron emission tomography imaging

The clinical presentation differences corroborate with brain atrophy and glucose hypometabolic patterns that are distinctive in extent and location between young- and late-onset Alzheimer's disease. On magnetic resonance imaging (MRI), young-onset Alzheimer's disease shows greater neocortical atrophy, particularly in parietal cortex, with preserved hippocampal volumes relative to LOAD (5). In LPA, MRI shows atrophy and decreased metabolism in the left temporo-parietal junction, while in PCA presentation, neuroimaging shows predominant areas of atrophy and hypometabolism from parieto-occipital cortex. Patients with the behavioural/dysexecutive variant of Alzheimer's disease manifest mild prefrontal atrophy, associated to moderate bilateral atrophy in temporoparietal regions. MRI studies suggest that functional connectivity changes differ in young- and late-onset Alzheimer's disease, the former being mainly driven by an early involvement of fronto-parietal networks (6). Progressive changes of neural networks are present before neuronal loss and regional atrophy and could contribute to the occurrence

of non-cognitive inaugural complaint before the onset of more classic cortical cognitive signs. This hypothesis will need to be tested in dedicated studies including imaging data.

Pathophysiological biomarkers

For young patients with an atypical non-amnesic presentation, the diagnosis of Alzheimer's disease is possible by using pathophysiological biomarkers such as cerebrospinal fluid (CSF) biomarkers or amyloid/tau positron emission tomography (PET) imaging.

Cerebrospinal Fluid (CSF) biomarkers

The profile of CSF biomarkers is the same: amyloid β 42 ($A\beta$) peptide levels are decreased, and total tau and phospho-tau levels are increased in CSF. Some studies suggest phenotypic variations in these CSF biomarkers, particularly lower tau levels in PCA (7), but this has not been confirmed across studies and with neuropathology.

Amyloid and tau PET biomarkers

The extent and distribution of tau pathology measured by PET differed between young- and late-onset Alzheimer's disease, with tau aggregation in widespread neocortical

regions (prefrontal and parietal cortex) in young-onset Alzheimer's disease while the pattern of tau deposition was more confined to the temporal regions in late-onset Alzheimer's disease, in line with neuropathological studies showing that damage to limbic structures may be a prominent feature of late but not of young-onset Alzheimer's disease (8). The regional pattern of tau pathology measured by PET was congruent with clinical presentation of the disease: high uptake was found in left temporo-parietal cortex in LPA and in parieto-occipital cortex in PCA. Similarly, people with the behavioural/dysexecutive variant of Alzheimer's disease exhibit temporoparietal pattern of tau uptake. The tau PET imaging pattern was inversely correlated with regional cortical hypometabolism assessed by FDG-PET. In addition, PET imaging confirms neuropathological studies, showing that the tauopathy is initially more severe and progresses faster in young-onset Alzheimer's disease than late-onset, supporting the idea that the disease is more aggressive in individuals with young-onset (9).

In contrast to the regional tau accumulation revealed by PET imaging, amyloid deposition was present diffusely throughout the neocortex, independent of clinical presentation and with no differences between young- and late-onset (10). Amyloid PET is especially useful in the differentiation of young-onset Alzheimer's disease from other dementias of early-onset.

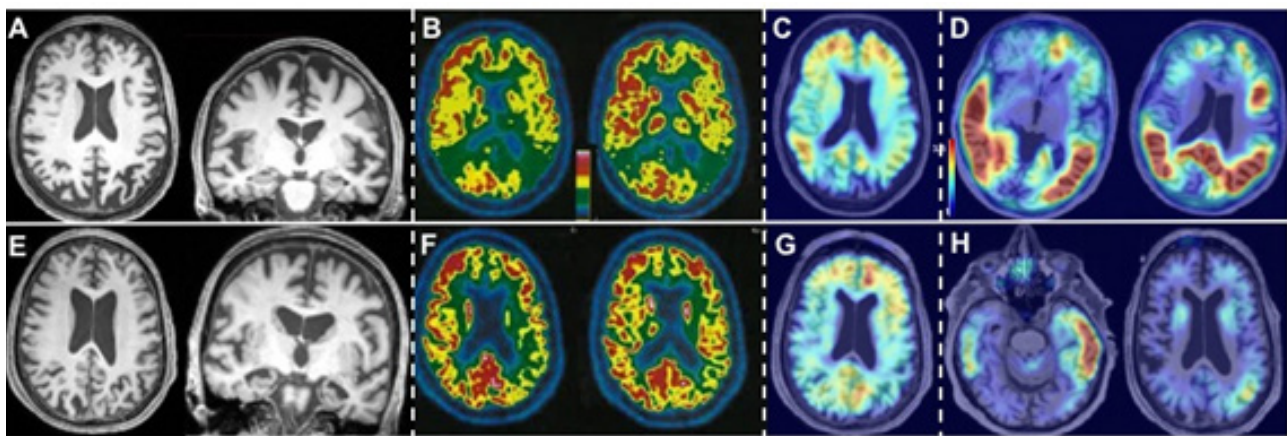


Illustration of the imaging features in a young and an older patient with Alzheimer's disease.

Top row: 53-year-old patient with Alzheimer's disease (CDR=0.5, estimated disease duration = 3 years). Bottom row: 80-year-old patient with Alzheimer's disease (CDR = 0.5, estimated disease duration = 6 years). Brain MRI shows a biparietal atrophy, with relatively preserved hippocampi in the young-onset patient (A), and a more pronounced hippocampal atrophy in the late-onset patient (E). FDG-PET shows a marked parietal hypometabolism in young-onset Alzheimer's disease (B), which is less pronounced in late-onset (F). The pattern of amyloid deposition is comparable in young- and late-onset patients (C, G). Tau tracer binding is more diffuse and more pronounced in the young-onset patient, extending to the temporo-parietal cortex, while it remains more restricted to the temporal lobes in the patient with late-onset dementia (D, H).

The amyloid and tau PET images are from the Shatau7-IMATAU study funded by the French Ministry of Health (PHRC-2013-0919), CEA, Fondation pour la recherche sur la maladie d'Alzheimer, Institut de Recherches Internationales Servier, France-Alzheimer.

Genetic: Autosomal dominant transmission

Familial Alzheimer's disease with autosomal dominant transmission is rare, only 1.6% of the total young-onset population carries a presenilin 1 (PSEN1), presenilin 2 (PSEN2), or amyloid precursor protein (APP) gene mutation (11). These three pathogenic mutations, which lead to aberrant cleavage or aggregation of the APP, explain three quarters of autosomal dominant cases: Dominant Alzheimer's disease: (PSEN1 in 52% of cases), APP (mutation in 9% and duplication in 7%) and PSEN2 in 6% (12). In these genetic forms, Alzheimer's disease most often begins before the age of 60 with a typical hippocampal amnesia in 84% of cases, but atypical cognitive forms are also described and should not be ignored, such as spastic paraparesis, early myoclonus, seizures, dysarthria, pseudobulbar affect, more extensive amyloid angiopathy.

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Therapeutic management

It is crucial to diagnose young-onset Alzheimer's disease as early as possible, in order to provide the most appropriate care, such as specific medication based on acetylcholinesterase inhibitors or memantine, rehabilitation, adaptation of the workspace when possible and also to avoid the prescription of contraindicated treatment such as anticholinergic antidepressants. The consideration of medico-social and psychosocial complications is essential for young patients, who often still have a professional activity and young children.

Moreover, the early diagnosis of young-onset Alzheimer's disease is a challenge to enable these people to participate in therapeutic trials, as their symptoms are often too pronounced at the time of diagnosis to be included.

Expert essay

Alzheimer's disease diagnosis in Down syndrome: challenges and opportunities

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Down syndrome is the most frequent cause of intellectual disability of genetic origin. There are approximately 5.8 million people living with Down syndrome in the world. The life expectancy of adults with Down syndrome has dramatically increased over the last decades due to improved healthcare, and now approaches 60 years of age in high income countries (1). Consequently, age-associated comorbidities are emerging, most importantly Alzheimer's disease (2).

Virtually all adults with Down syndrome develop the hallmarks of Alzheimer's disease pathology by age 40, and the lifetime risk of dementia is estimated to be well over 90% (3). Dementia is rare before the age of 40, but its incidence and prevalence exponentially increase thereafter to over 80% in those over the age of 65 (Figure 1) with a median age at dementia diagnosis ranging between the ages of 53 and 55 (3,4). Dementia due to Alzheimer's disease is now the main cause of death in adults with Down syndrome. This strong association is mainly due to the triplication of amyloid precursor protein gene (1–3).

Clinical challenges

The clinical presentation of Alzheimer's disease in Down syndrome is now recognised as similar to that of sporadic Alzheimer's disease, with early declines in episodic memory as well as declines in attention and in executive functions. These are followed by declines in other cognitive abilities and the development of functional, behavioural, and neurological symptoms (5,6). The diagnosis of mild cognitive impairment or prodromal Alzheimer's disease requires a change in cognition reported by the carer (cognitive complaints by adults with Down syndrome are rare) based on decline from previous performance. As in the general population, dementia is diagnosed when activities of daily living are clearly affected and need to have changed from premorbid functioning. The variable degree of premorbid intellectual disability problematises these definitions. First, there are different degrees of cognitive functioning due to the variable levels of intellectual disability, which complicates the formal definition of mild cognitive impairment or prodromal Alzheimer's disease. Similarly,

many individuals with Down syndrome have longstanding impairments in daily activities, complicating the definition of Alzheimer's disease dementia. Prodromal Alzheimer's disease might impact on functionality earlier in Down syndrome than in the general population due to lower cognitive and functional reserve (1).

Clinicians with expertise in the diagnosis of Alzheimer's disease are able to make accurate diagnoses despite the difficulties in assessing the Alzheimer's disease-related cognitive impairment and the absence of validated operationalised clinical diagnostic criteria, if they consider the individual's baseline functioning, and exclude other causes of decline (1). People with Down syndrome usually score at floor in the neuropsychological test batteries used in the general population; therefore, adapted tests are required (1,2). Using these adapted tests, recent research suggests that population norms are feasible if the subjects are stratified by the level of intellectual disability (7). Another important recommendation is to consider the within-person longitudinal change on tests if data is available on the personal best level of achievement. One limitation of the most current adapted tests, however, is that most adults with Down syndrome with severe intellectual disability cannot perform these tests. Other measures of cognitive functioning and dementia symptoms should be used for these individuals, including carer reported tools (1).

Comorbidities frequently found in adults with Down syndrome pose another important clinical challenge. Early symptoms can be mistaken as part of lifelong impairments or obscured by coexisting medical comorbidities that might affect cognition, such as obstructive sleep apnoea, hypothyroidism and depression. Conversely, given the early age of onset of dementia, the differential diagnosis rarely includes other neurodegenerative dementias (1,2).

Finally, the lack of awareness from families, carers and clinicians represents another important challenge, which is currently delaying or impeding Alzheimer's disease diagnoses in adults with Down syndrome. Consultations often only occur when activities of daily living are substantially

affected, or when behavioural problems emerge, hence early descriptions of a behavioural or frontal subtype as the main clinical presentation in Down syndrome.

Alzheimer's disease biomarkers offer new opportunities

Biomarkers are revolutionising the diagnosis of Alzheimer's disease in the general population. Several biomarkers have been approved by regulatory agencies and are increasingly included in clinical guidelines. In Down syndrome, however, promising results on these biomarkers have yet to be applied in clinical diagnosis.

There are few studies with cerebrospinal fluid biomarkers in Down syndrome, but all have consistently shown the typical biochemical Alzheimer's disease signature with a 50% reduction in the β -amyloid 42/40 ratio and a two-fold increase phosphorylated tau levels in symptomatic patients (8).

Blood-based biomarkers are now feasible due to the development of ultrasensitive technologies, and well tolerated in individuals with Down syndrome. Plasma neurofilament light (NfL) levels have excellent diagnostic and prognostic performances (8–10). NfL levels are not specific to Alzheimer's disease, but they are highly indicative of symptomatic Alzheimer's disease in the context of Down syndrome (8–10). This is due to the aforementioned fact that other neurodegenerative disorders are exceedingly rare. Novel plasma phosphorylated-tau assays have been recently developed and have high accuracy for Alzheimer's disease diagnosis (1). Adults with Down syndrome have higher plasma A β concentrations than euploid controls, but these biomarkers have not yet proven to be useful for diagnosing symptomatic Alzheimer's disease (1). Of note, there are no reports

in Down syndrome with the novel mass spectrometry techniques that accurately detect brain amyloidosis in sporadic Alzheimer's disease.

Imaging biomarkers have also been used in the Down Syndrome population. The atrophy pattern in the MRI and the brain hypometabolism associated with Alzheimer's disease shows the same regional pattern of hypometabolism in Down syndrome as seen in sporadic Alzheimer's disease involving the medial temporal, parietal, precuneus and posterior cingulate regions (1–3). Amyloid PET studies also show a similar pattern of amyloid deposition to that described in sporadic Alzheimer's disease (1–3). There are only a very small number of studies using tau PET tracers in Down Syndrome, but the available data also shows a typical Alzheimer's disease pattern (1).

Of note, these biomarkers changes begin 20 years before symptom onset and the natural history of Alzheimer's disease in Down syndrome follows a predictable sequence of events in biomarker changes in a strikingly similar order and timing to that described in autosomal dominant Alzheimer's disease (3).

In summary, there are challenges leading to clinical underdiagnosis and/or misdiagnosis. However, accurate clinical diagnoses are possible, and biomarkers have potential for Alzheimer's disease diagnosis in this population. In the future, population-based screening for Alzheimer's disease in Down syndrome may substantially increase detection. Such programmes should target those adults with Down syndrome over 35–40 years of age (1), and include plasma biomarkers, which have the potential to become useful and cost-effective screening tools. Accurate diagnoses are the essential first step towards timely access to treatment (which is now becoming available) and care planning.

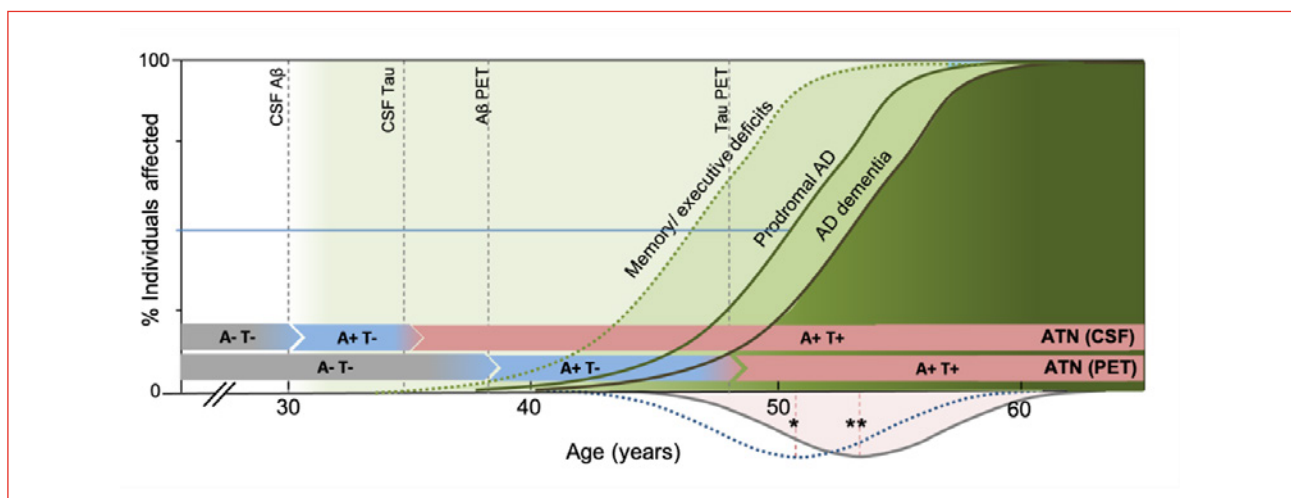


Figure 1. The arrows reflect the timing for the earliest changes in CSF and PET biomarkers. The model shows the clinical progression of Alzheimer's disease in people with Down Syndrome. Subtle memory/executive deficits may start from age 35, prodromal Alzheimer's disease occurs at a median age of 51 years (*) and dementia at age 54 (**) years of age. The Gaussians below the X-axis reflect density of prodromal and Alzheimer's disease dementia diagnosis in Fortea et al. (3) The vertical dotted lines reflect the earliest biomarker changes for the amyloid and tau biomarkers in the same paper.

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Conclusions

Young-onset dementia can be seen as particularly cruel as it strikes individuals before the age of 65, young people in their prime with jobs, children and an active social and physical life. It contradicts what most people associate with this age group, namely, that it is an 'old person' condition that young people need not concern themselves with.

Although half of these cases are attributable to the onset of various dementias, other rarer underlying causes may be at play when young-onset is diagnosed. As some of these causes are treatable or reversible (for example, a person who has suffered repeated head trauma or abused alcohol and drugs) referring these individuals to specialised centres, such as memory clinics or a hospital's neurology department, is especially critical.

This is part of the reason a young-onset diagnosis can be an especially long, complex and difficult journey. By ensuring they are not misdiagnosed, which further exacerbating the symptoms, pinpointing these other factors is necessary to orient the management of the case. This includes providing the appropriate and effective therapies or medication in a timely manner.

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