4th International Alzheimer's Disease Conference

مؤتمر ألزهايمر الدولي الرابع ٢٠٢٠

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Early Onset Dementia

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Young-Onset Dementia

•Young-onset dementia (YOD) is a devastating condition that typically afflicts patients between the ages 45-64 years with approx prevalence of 67-98 per 100,000 people.

•Common symptoms include behavioral changes, psychiatric manifestations, and cognitive decline.

•Eventually leads to a deterioration of day-to-day function, and causes significant caregiver burden.

•YOD is frequently misdiagnosed.

•In order to avoid misdiagnosis, it is critically important to attain a thorough medical history, collateral behavior history from an informant, and detailed family history in advance of ordering additional studies.

•In some cases of YOD, treatment can completely reverse symptoms while in others, early diagnosis and intervention can improve quality of life and inform decisions regarding family planning.

Characteristics of EOAD compared with LOAD

◆ There is a large proportion of nonamnestic phenotypic variants (logopenic variant primary progressive aphasia, posterior cortical atrophy, behavioral/dysexecutive, acalculia, corticobasal syndrome)

◆ About 1 in 10 patients has an autosomal dominant familial Alzheimer disease (PSEN1, PSEN2, APP), and there is a high polygenic risk score

◆ There is a higher APOE4 frequency in the amnestic early-onset Alzheimer disease but less so in variant phenotypes

◆ There is more aggressive course with high rate of mortality

◆ Delay in diagnosis of about 1.6 years

◆ Higher prevalence of traumatic brain injury (which lowers age of onset) and lower vascular risk factors

Characteristics of EOAD compared with LOAD, continued

◆ There is hippocampal sparing and less mesial temporal lobe disease

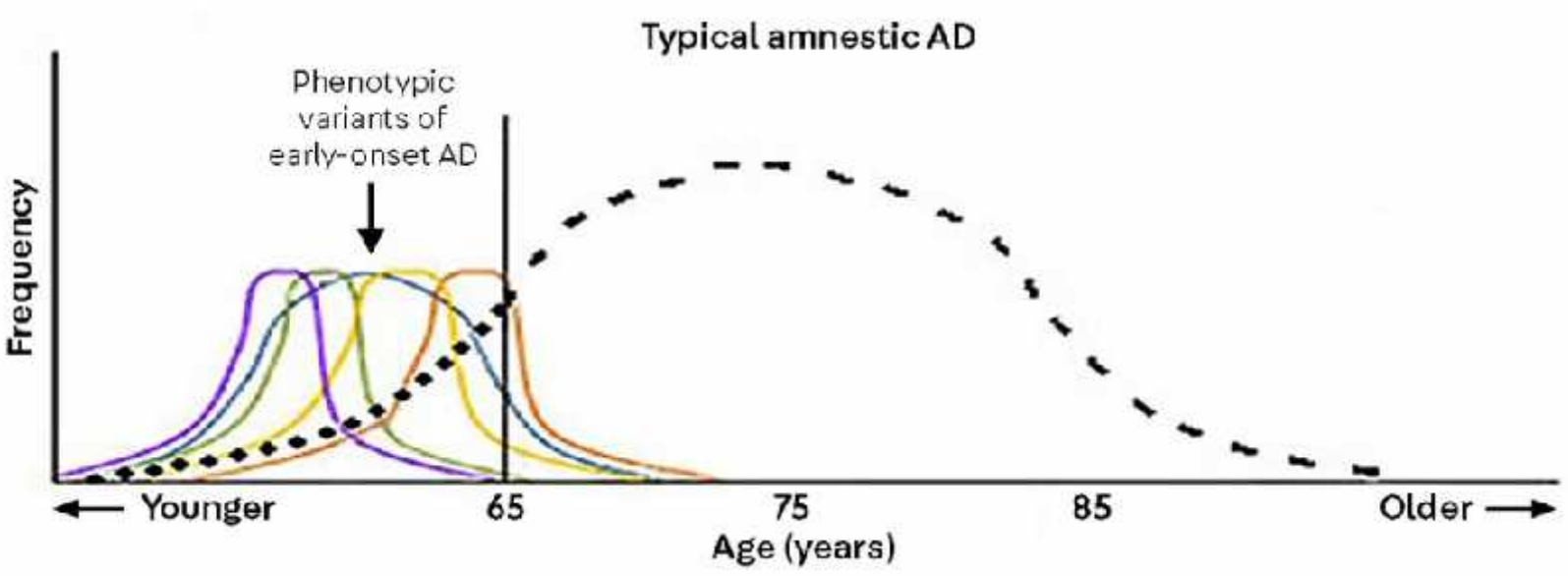
◆ Overall there is less semantic memory impairment and greater attention, executive, praxis, and visuospatial difficulties

◆ Greater psychosocial problems (unexpected midlife “out-of-step” loss; continued work, financial, family responsibilities; retained insight with depression, anxiety, suicide risk)

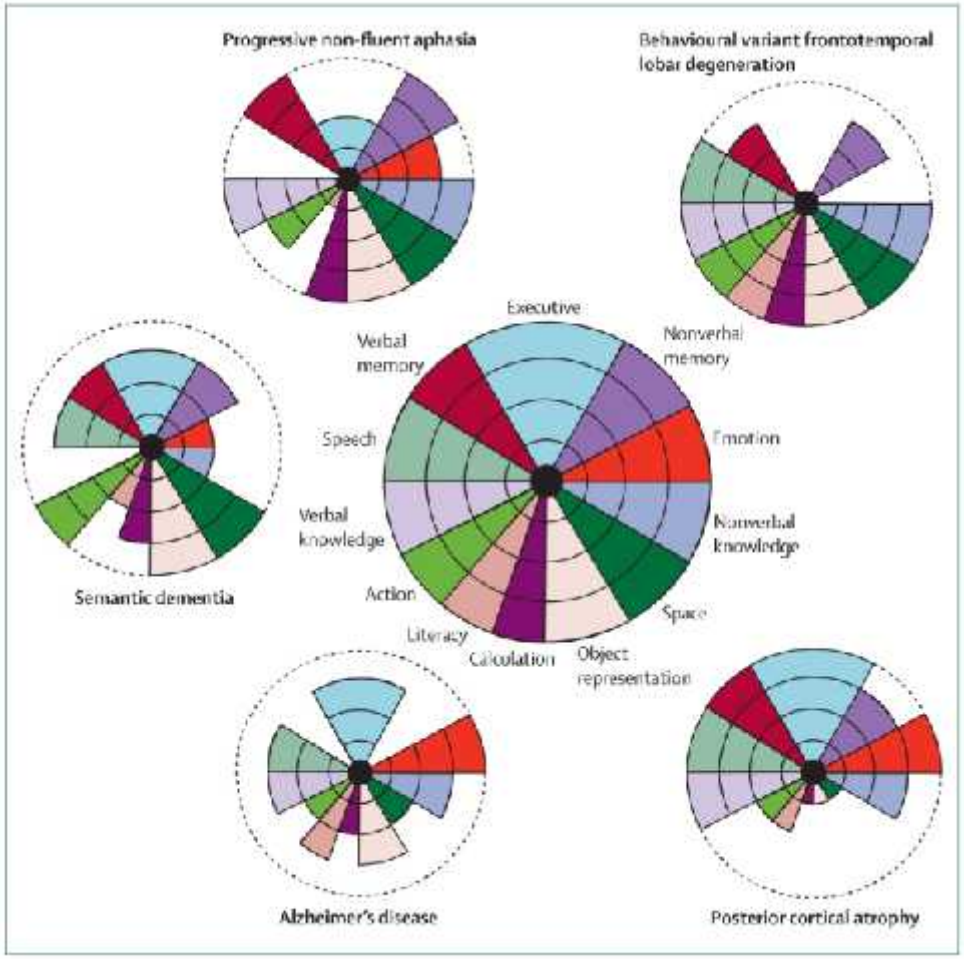
◆ Greater posterior (parietal, temporoparietal junction) neocortical atrophy and hypometabolism versus temporal atrophy and hypometabolism

◆ Higher burden of tau/neurofibrillary tangles per gray matter atrophy and stage of dementia, especially in focal phenotypic areas (reflected in tau imaging)

◆ Greater involvement of white matter tracts in posterior association areas and frontoparietal networks than the default mode network



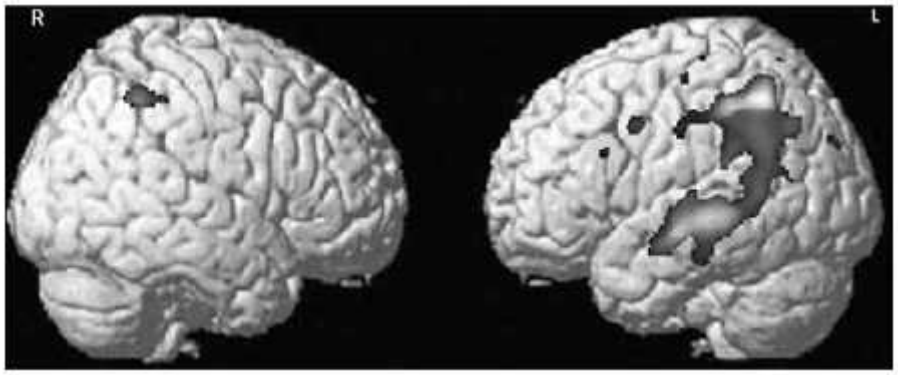
Phenotypic variants of early-onset Alzheimer disease **compared to typical amnestic Alzheimer disease** across the age spectrum. The different colored lines in the graph are meant to represent the probable distributions of different phenotypic variants of early-onset Alzheimer disease, such as **posterior cortical atrophy**, **logopenic variant primary progressive aphasia**, the **behavioral/dysexecutive variant**, and **the acalculic variant**


Progressive non-fluent aphasia
Behavioural variant frontotemporal lobar degeneration
Executive
Verbal memory
Nonverbal memory
Speech
Emotion
Verbal knowledge
Nonverbal knowledge
Action
Space
Literacy
Calculation
Object representation
Semantic dementia
Alzheimer's disease
Posterior cortical atrophy

Logopenic Variant Primary Progressive Apahsia

- An insidious onset and progressive disorder of language
- Word-finding difficulty with frequent word-finding pauses; may have circumlocutions (intermediate fluency between the nonfluent/agrammatic and semantic primary progressive aphasia variants)
- Overall decreased verbal output and slower rate
- Decreased word retrieval with phonologic paraphasias (errors)
- Disproportionately decreased repetition of sentences (hallmark finding)
- Decreased comprehension for long (not complex) sentences but not for words
- Preserved grammar (although it may be syntactically simple)
- Preserved motor articulation
- Other evidence of decreased phonologic store (eg, decreased digit or word span)
- Left posterior temporal/inferior parietal dysfunction on neuroimaging

Logopenic Variant Primary Progressive Apahsia



Voxel-based morphometry of parietal overlap of early-onset Alzheimer disease phenotypes, showing cortical atrophy in 10 patients with logopenic variant primary progressive aphasia compared to 64 normal controls.

The dark regions show the foci of greater atrophy in logopenic variant primary progressive aphasia asymmetrically affecting the left parietal and posterior temporal region in the left hemisphere with much less involvement of the right hemisphere.

Posterior Cortical Atrophy Variant of Young Onset Dementia

Complex Visual Disorders among PCA Patients (approximate order of frequency)

- Alexia (> oral difficulty)
- Balint's (whole or partial), especially optic ataxia
- Visual object agnosia
- Environmental disorientation
- Dressing apraxia/other spatial
- Prosopagnosia (apperceptive)
- Color perception problems
- Hemispatial neglect or visual field constriction on the left

Adapted from Mendez et al, 2002[49]

Characteristics of the Acalculia Variant of Early-onset Alzheimer Disease

Acalculia

- Primary anarithmia not due to language or spatial impairment
- Difficulty with simple written calculations with transcoding and syntax errors

Other Elements of Gerstmann Syndrome

- Finger (digit) agnosia
- Right-left disorientation
- Agraphia (transitional with linguistic elements)

Alexia With Agraphia (Left)

Ideomotor Apraxia

- Both transitive (with pretend tool use) and intransitive (gestural-symbolic)
- Difficulty with imitation as well as pantomime

Disorders of the Dorsal Visual Stream

- Visuospatial localization
- Depth perception

Young-Onset Dementia

•The differential diagnosis within YOD is extensive, but can be categorized as:

•early-onset forms of adult neurodegenerative conditions:
- •AD the most common cause

• late-onset forms of childhood neurodegenerative conditions: mostly in younger than 35
- •such as mitochondrial disorders, lysosomal storage disorders, and leukodystrophies

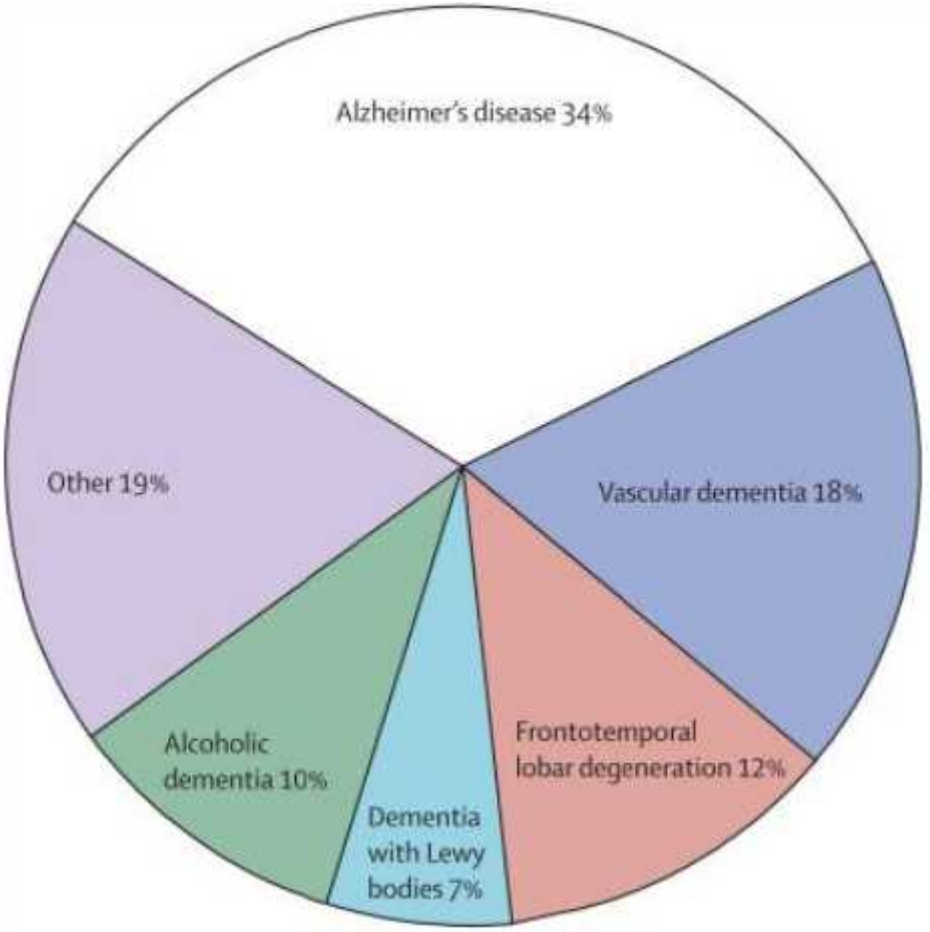
•reversible conditions: Perhaps the most important category:
- •inflammatory, infectious, toxic, and metabolic etiologies

•Several of the YODs have hereditary forms, and genetic testing is an increasingly important method for confirming diagnoses and evaluating risk in family members.

Early-Onset Forms of Adult Neurodegenerative Disorders

- Alzheimers Disease
- Vascular Dementia
  - Cerebrovascular Disease
  - Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts
  - and Leukoencephalopathy (CADISIL)
- Fronto Temporal Dementia
- Alpha synuclein pathology
  - Lewy body dementia (LBD)
  - Multi system atrophy
- Huntingtons Disease
- Creutzfeldt-Jakob disease
- Chronic Traumatic encephalopathy
- Fahr´s disease

Early-Onset Forms of Adult Neurodegenerative Disorders



Late-Onset Forms of Childhood Neurodegenerative Disorders

- **Mitocondrial disorders**
  - mitochondrial encephalopathy with lactic acidosis and stoke-like episodes (MELAS)
  - myoclonic epilepsy with ragged red fibers (MERRF)
  - Kearns-Sayre syndrome
- **Lysosomal storage disorders**
  - Tau Sachs disease
  - Gaucher´s disease type 2 and 3
  - Nieman-Pick disease type C
  - Fabry´s disease
  - Kuff´s disease
- **Leukodystrophies**
  - adrenoleukodystrophy
  - metachromic leukodystrophy
  - Alexander disease
  - leukoencephalopathy with vanishing white matter,
  - Pelizaeus-Merzbacher disease
  - adult polyglucosan body disease
  - cerebrotendinous xanthomatosis

Reversible Forms of Young-Onset Dementia

The inflammatory causes of YOD include:

Multiple sclerosis is classically characterized by multi-focal neurological deficits dispersed in time, which may include cognitive deficits associated with sensory and motor dysfunction, changes in vision, and ataxia.

Neurosarcoidosis may be characterized by neuropathy, neuroendocrine dysfunction, focal neurological deficits, myelopathy, hydrocephalus, and meningitis.

Paraneoplastic and autoimmune limbic encephalitis is associated with auto-antibodies or the inflammatory response to tumors outside the nervous system and may cause changes in cognition, mood, behavior, and seizures.

Reversible Forms of Young-Onset Dementia

The infectious etiologies of YOD include HIV dementia, neurosyphilis, Whipple disease, and progressive multifocal leukoencephalopathy (PML).

In addition to cognitive decline, these disorders have the following additional symptoms: mood disorder and systemic illness in HIV dementia; meningitis and tabes dorsalis in neurosyphilis; arthralgia, GI symptoms, oculomasticatory myorhythmia, and ataxia in Whipple disease; and changes in vision, hemiparesis, and ataxia in PML.

Reversible Forms of Young-Onset Dementia

Toxic and metabolic causes of YOD are numerous and include alcohol, other drugs of abuse, and heavy metal poisoning.

In addition to changes in cognition, symptoms of abuse of alcohol and other drugs include psychiatric symptoms, ataxia, tremor, blurred vision, dysarthria, respiratory difficulties, and coma. Non-cognitive symptoms of heavy metal poisoning include psychiatric symptoms, distal sensory and motor neuropathy, GI symptoms, and weakness.

The toxic encephalopathies are most often diagnosed using blood or urine levels of the toxin and described neuroimaging features.

Reversible Forms of Young-Onset Dementia

Metabolic encephalopathy may be caused by excess ammonia in hepatic encephalopathy, uremia, hyponatremia, or hypernatremia.

Symptoms include confusion and agitation with associated motor features.

The diagnosis typically relies on routine laboratory studies,

Reversible Forms of Young-Onset Dementia

Endocrinopathies that may cause YOD are glucose dysregulation, thyroid or parathyroid dysfunction, Addison's disease, and Cushing's disease. Symptoms include confusion with weakness or fatigue, and other symptoms specific to each endocrinopathy.

Nutritional deficiencies in B12, thiamine, **and niacin** can also lead to YOD.

Vitamin B12 deficiency may cause cognitive dysfunction with associated megaloblastic anemia, jaundice, fatigue, atrophic glossitis, or subacute combined degeneration of the spinal cord.

Thiamine deficiency may result in confusion with prominent anterograde memory deficits, ataxia, and ophthalmoplegia. Dementia associated with niacin deficiency is associated with dermatitis and diarrhea. Diagnosis most often relies on the combination of laboratory assessment of vitamin levels and neuroimaging. Treatment is supplementation and nutritional support.

Reversible Forms of Young-Onset Dementia

There are several other potentially reversible causes of YOD.

Wilson's disease is due to mutation of ATP7B gene which inhibits copper metabolism, leading to cognitive dysfunction with prominent psychiatric features, associated movement disorders, liver disease, and Kayser-Fleischer rings on ophthalmological exam.

Diagnostic laboratory features are low serum copper and ceruloplasmin with high urinary copper.

Transient epileptic amnesia (TEA) presents with recurrent episodes of anterograde memory loss.

EEG shows temporal lobe spikes, and neuroimaging often reveals atrophy of the hippocampus.

Reversible Forms of Young-Onset Dementia

Obstructive sleep apnea (OSA)
may present as cognitive dysfunction as a result of hypoxemia or sleep deprivation. It is also an independent risk factor for stroke and, as such, may contribute to vascular dementia.

Diagnosis is confirmed with polysomnography.

Normal pressure hydrocephalus (NPH) can also present as dementia in variable combination with gait disturbance and urinary incontinence.

After the diagnosis is relatively confirmed via neuroimaging and ancillary testing.

Reversible Forms of Young-Onset Dementia

It is important to recognize that some of the disorders described as potentially reversible, including multiple sclerosis, progressive multifocal leukoencephalopathy, HIV dementia, and thiamine deficiency, and may cause irreversible damage to the nervous system in advance of the diagnosis and intervention.

Reversible causes of YOD should be investigated early and thoroughly in all cases of YOD, given the implications for patients and caregivers.

Clinical Assessment

The first step towards accurate diagnosis is performing a thorough clinical assessment.

This involves obtaining a clinical history including symptoms in all cognitive domains (not exclusively memory), behavioral features and psychiatric history, degree of functional impairment, temporal profile of mode of onset and progression of symptoms, past medical history, social history including educational and occupational attainment, and family history of neuropsychiatic illness.

Other important points may include specific dementia risk factors including head injury with loss of consciousness or alcohol/drug exposure.

It is critically important to obtain a collateral history from a reliable informant, as patients may have little insight into their deficits or forget important historical details

Clinical Assessment

Once this information is gathered, the clinician should perform a thorough **neurological exam** with special attention to pyramidal, extrapyramidal, and cerebellar signs.

Bedside cognitive assessment with screening instruments such as the Mini Mental State Examination or the Montreal Cognitive Assessment and **formal neuropsychological testing** are valuable to clarify the affected cognitive domains.

The combination of historical details, cognitive and behavioral features, and findings on the neurological examination guide the generation of diagnostic hypotheses related to the presumed underlying neuroanatomy.

This **“dementia-plus” algorithm** **has been advocated and provides a useful framework for the clinical assessment of YOD**

Dementia plus syndromes and associated diseases—neurological features

Ataxia

Spinocerebellar ataxia (particularly types 2, 12, and 17),
paraneoplastic diseases, prion diseases (particularly familial forms and variant CJD), DRPLA (common in Japan), fragile x-associated tremor ataxia syndrome, familial British and Danish dementias, mitochondrial disorders, superficial siderosis, neuronal ceroid lipofuscinosis (Kuf's disease), Niemann-Pick disease type C, multiple system atrophy (dementia usually mild, if present), Alexander's disease, and multiple sclerosis

Pyramidal signs

Multiple sclerosis, frontotemporal lobar degeneration with motor neuron disease, Alzheimer's disease (some presenilin mutations), spinocerebellar ataxias, phenylketonuria, familial British and Danish dementias, hereditary spastic paraparesis (SPG4), adrenoleukodystrophy, vanishing white matter disease, polyglucosan body disease, polycystic lipomembranous sclerosing leukoencephalopathy (Nasu-Hakola disease)

Dystonia/chorea

Huntington's disease (and Huntington's disease-like syndromes 1–3), Kuf's disease (characteristic facial dyskinesia), Wilson's disease, neuroacanthocytosis, pantothenate kinase-associated neurodegeneration (neurodegeneration with brain iron accumulation), Lesch-Nyhan syndrome, DRPLA, corticobasal degeneration, neuroferritinopathy, antiNMDA receptor-mediated limbic encephalitis, variant CJD

Dementia plus syndromes and associated diseases—neurological features

Bucco-lingual mutilation
Neuroacanthocytosis, Lesch-Nyhan syndrome

Akinetic-rigid syndrome
Lewy body disease (dementia with Lewy bodies and Parkinson's disease dementia), progressive supranuclear palsy, multiple system atrophy (dementia usually mild, if present), Huntington's disease (particularly juvenile onset), corticobasal degeneration, dementia pugilistica, Wilson's disease, pantothenate kinase-associated neurodegeneration (neurodegeneration with brain iron accumulation), frontotemporal lobar degeneration with parkinsonism-17, Alzheimer's disease (usually advanced)

Peripheral neuropathy
Neuroacanthocytosis, cerebrotendinous xanthomatosis, HIV infection, giant axonal neuropathy, alcohol-related diseases, metachromatic leukodystrophy, porphyria, adrenoleukodystrophy, GM2 gangliosidosis, polyglucosan body disease, Krabbe's disease, sialidosis, Fabry's disease, mitochondrial disorders, spinocerebellar ataxias (particularly type 3)

Myoclonus or early seizures
Prion disease, Alzheimer's disease, Lewy body disease, DRPLA, mitochondrial disorders, Gaucher's disease, GM2 gangliosidosis, neuroserpinopathy, polycystic lipomembranous sclerosing leukoencephalopathy, subacute sclerosing panencephalitis, progressive myoclonic epilepsy syndromes, Kuf's disease, Lafora body disease, sialidosis

Dementia plus syndromes and associated diseases—neurological features

Gaze palsy

Niemann Pick disease type C (vertical supranuclear; early downgaze loss), Gaucher's disease (horizontal supranuclear), progressive supranuclear palsy (vertical supranuclear), mitochondrial disorders, spinocerebellar ataxias (particularly type 2), paraneoplastic disorders, Whipple's disease

Deafness

Superficial siderosis, mitochondrial disorders, familial Danish dementia, alpha mannosidosis, sialidosis

Dysautonomia

Lewy body disease, multiple system atrophy, prion disease (fatal familial insomnia), porphyria, adrenoleukodystrophy, anti-NMDA receptor-mediated limbic encephalitis The dementia plus syndromes describe patterns of cognitive impairment (dementia) plus additional neurological or systemic features that aid investigation and diagnosis of the underlying disease process. This list cannot be comprehensive. Note that vascular disease, structural disorders, and (para) neoplastic disease can be associated with a wide range of presentations. DRPLA=dentatorubral-pallidoluysian atrophy. CJD=Creutzfeldt-Jakob disease.

Dementia plus syndrome and associated diseases – systemic features

Cataracts
Myotonic dystrophy, cerebrotendinous xanthomatosis, mitochondrial disorders, familial Danish dementia

Splenomegaly
Niemann-Pick disease type C, Gaucher's disease

Tendon xanthomas
Cerebrotendinous xanthomatosis

Bone cysts
Polycystic lipomembranous sclerosing leucoencephalopathy

Paget's disease
Valosin-associated frontotemporal lobar degeneration

Dementia plus syndrome and associated diseases – systemic features, con't

Renal impairment
Fabry's disease, Lesch-Nyhan syndrome, mitochondrial disorders

Hepatic dysfunction
Wilson's disease, Gaucher's disease, mitochondrial disorders

Respiratory failure
Frontotemporal lobar degeneration and motor neuron disease, Perry syndrome, mitochondrial disease (eg, POLG), anti-NMDA receptor-mediated limbic encephalitis

Gastrointestinal dysfunction
Coeliac disease, Whipple's disease, porphyria

Anaemia
Vitamin B12 deficiency, neuroacanthocytosis (McLeod's syndrome), Wilson's disease, Gaucher's disease

Skin lesions
Behcet's disease, systemic vasculitides and connective tissue disease, Fabry's disease

Metabolic or infectious crises
Vanishing white matter disease, Alexander's disease, ornithine transcarbamylase deficiency, alpha mannosidosis, porphyria

Hyponatraemia
VGKC limbic encephalitis

Laboratory investigations

Laboratory investigations are important in the diagnosis of YOD; however a rational, **stepwise approach** is advised.

It is advisable to perform **simple tests before those that are complex and invasive.**

Blood tests may be useful in diagnosing toxic/metabolic encephalopathies, infectious etiologies such as HIV or syphilis, and autoimmune illnesses.

All patients with YOD should have neuroimaging (preferably MRI) and **possibly CSF analysis** according to professional organization guidelines. Patterns of brain atrophy and signal change on a variety of MRI sequences are useful in narrowing the differential diagnosis.

In patients who demonstrate minimal changes on MRI, **FDG-PET imaging may be a useful adjunct to detect regions of hypometabolism. And now we have amyloid and tau PET.**

Laboratory investigations

CSF analysis may facilitate the identification of infectious or inflammatory etiologies of YOD, plus help confirm Alzheimer´s disease.

Neurophysiology studies such as electroencephalography (EEG), electromyography (EMG), and nerve conduction studies (NCS) can reveal associated seizure activity, myopathy, and neuropathy, respectively.

Tissue biopsy may be helpful to diagnose mitochondrial disorders via muscle biopsy and lysosomal storage disorders or leukodystrophies via enzyme assay of skin fibroblasts or leukocytes. **Cerebral biopsy**, although not often performed, has proven to be a relatively safe and efficacious method of diagnosing dementia, and should be considered if there is even a low index of suspicion for a potentially treatable disease.

Genetic testing, although cost-prohibitive if not ordered selectively, is available to confirm many YOD diagnoses for patients, as well as to predict susceptibility in family members. If families choose to undergo genetic testing, it should be preceded by formal genetic counseling

EOAD: Key Points

EOAD is not just LOAD at a younger age; there are substantial differences between these two categories of Alzheimer's disease.

• Compared to LOAD, EOAD has greater neocortical pathology, particularly in parietal cortex, greater tau compared to amyloid burden, and less hippocampal disease.

• Up to 50% or more of patients with EOAD have non-amnestic, phenotypic variants, including logopenic variant primary progressive aphasia, posterior cortical atrophy, progressive ideomotor apraxia, behavioral/dysexecutive AD, corticobasal syndrome, and others. These may be conceptualized as "Type 2 AD."

• Compared to LOAD, the phenotypic variants of EOAD preferentially involve alternate, fronto-parietal neural networks rather than the posterior default mode network.

• The management of EOAD differs from LOAD in the emphasis on targeted cognitive interventions and age-appropriate psychosocial support.

Talk based on these articles

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Lancet Neurol. 2010 August ; 9(8): 793–806. doi:10.1016/S1474-4422(10)70159-9.

The diagnosis of young-onset dementia

Martin N Rossor, **Nick C Fox**, **Catherine J Mummery**, **Jonathan M Schott**, and **Jason D Warren**
Dementia Research Centre, Department of Neurodegeneration, UCL Institute of Neurology, Queen Square, London, UK (Prof M N Rossor FRCP, Prof N C Fox FRCP, C J Mummery FRCP, J M Schott MRCP, J D Warren FRACP)

Early-onset Alzheimer Disease and Its Variants

By Mario F. Mendez, MD, PhD, FAAN

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Young-Onset Dementia

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Early-Onset Alzheimer's Disease

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