Early-Onset Dementias

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Introduction

Early onset dementias sometimes arbitrarily refers to dementia becoming clinically manifested before age 65, and the term “young onset dementias” is used for onset before age 45 (Kelley et al, 2008). For the purpose of this document written for the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4), the terms will be used interchangeably, as was done by Martin Rossor in his latest review on the topic (Rossor et al, 2010). A brief literature review will highlight the difficulties encountered in the diagnosis and management of such

patients, with recommendations for discussions during the CCCDTD4 meeting of May 2012 in Montreal. The literature review is based on the expertise of the different authors, and the grading of recommendations is based on resources allocation rather than efficacy of treatments (Table 1; Guyatt et al, 2008).

Table 1

Grading of recommendations based on the American College of Chest Physicians Evidence-Based Practice Guidelines (8th Edition)

Grade 1 Can be applied uniformly to most patients
Grade 2 Suggestions require more judicious application

Early onset familial Alzheimer's disease (EOFAD)

This is the most well known group of persons with early onset dementia because of the autosomal dominance pattern of inheritance affecting first degree relatives, the high penetrance of the three known major mutations, which are looked for in genetics clinics, and the recent interest in the progression of biomarkers through the asymptomatic, mild cognitive impairment (MCI) and early dementia stages, studied as part of the Dominantly Inherited Alzheimer Network (DIAN) (http://dian-info.org/). It is hoped that studies such as this may lead to anti-amyloid and other drug trials in this group of under-treated patients and those at risk (i.e., presymptomatic carriers), since they could not previously be defined as "probable AD" under the old McKhann et al criteria where a lower age of 40 had been arbitrarily assigned to this condition (McKhann et al, 1984).

EOFAD has been extensively reviewed by Wu et al, (2012) and the highlights of this review are the following: early-onset familial Alzheimer's disease (EOFAD) is a condition that represents up to 5% of all the AD cases in clinical practice. To date, 230 mutations in presenilin (*PS1, PS2*) and amyloid precursor protein *(APP*) genes have

been identified in EOFAD. The mutations within these three genes (*PS1/PS2/APP*) affect a common pathogenic pathway in APP synthesis and proteolysis, which leads to excessive production of amyloid β (Aβ). For the most part, the clinical presentation of EOFAD is similar to that of sporadic AD. However, there are some distinctive features including early age at onset (AAO), positive family history, a variety of non-cognitive neurological symptoms and signs, and a more aggressive course. Despite relatively similar biochemical defects, there is marked phenotypic heterogeneity among different mutations of EOFAD. Clinical symptoms start at an earlier age for carriers of *PS1* mutations in comparison to those with *PS2* or *APP*. Studies in presymptomatic mutation carriers reveal amyloid pathological biomarker abnormalities including positive uptake of Pittsburgh Compound B on positron emission tomography (PET) and lowering of Aβ in cerebrospinal fluid (CSF) at least ten years before symptoms emerge.

Other causes of early onset dementias

The conditions most commonly reported in the recent medical literature as causes of early onset dementias are listed alphabetically in Table 1.

Table 1

Common causes of early-onset dementias

Alcoholic dementia

Alzheimer's disease (AD)

Cerebro-vascular disease (CVD)

Creutfeldt Jacob disease (CJD)

Dementia with Lewy Bodies (DLB)

Fronto-temporal dementia (FTD) or Frontotemporal lobar degeneration (FTLD)

Vascular Dementia

There are considerable variations between clinics specialized in early-onset dementias based on patterns of referrals. For instance Fronto-Temporal Lobar Degeneration (FTLD) was more common in the Manchester clinico-pathological study compared to other causes because of their interest in this condition (Snowden et al, 2011). In Canada, FTLD accounts for about 12% of referrals in those under age 70 to specialized dementia clinics.(Feldman, Levy, Hsiung et al, Neuroepidemiology 2003). Familial inheritance of FTLD is even stronger than AD, representing 10-20% of all FTLD encountered clinically. (Stevens M et al, Neurology 1998; Chow T et al, Arch Neuro 1999) To date, three genes have been identified to be responsible for the majority of autosomal dominant forms of FTLD: 1) microtubule-associated protein tau (MAPT), progranulin (GRN), and the C9ORF72 gene. (Hutton et al, Nature 1998; Baker et al, Nature 2006; DeJesus-Hernandez et al, Neuron 2011). Mutations in the valosin-containing protein (VCP), chromatin modifying protein 2B (CHMP2B), transactive DNA-binding protein (TARDBP) and fused-in-sarcoma (FUS) have also been identified as rare causes of familial FTLD (Rohrer JD and Warren JD, Curr Opin Neurol 24:542–549). Most FTLD cases have an age of onset in the 50's to 60's, but the reported range is highly variable from 29 to 81 years old, particularly in those with GRN or C9ORF72 mutations. (Hsiung 2007; Hsiung 2012).

The discovery of the various FTLD-causing mutations has largely been driven by the genomic analysis of subgroups of patients classified according to the heterogeneous pathologies underlying FTLD. These can be largely divided into two broad subgroups: Tau-positive cases (FTLD-Tau; can be associated with MAPT mutations) and Tau-negative cases with ubiquitin and TDP43 inclusions (FTLD-TDP; can be associated with GRN and VCP mutations, and C9ORF72 hexanucleotide repeat expansions) (Seelaar H, Rohrer JD, Pijnenburg YAL, et al. J Neurol Neurosurg Psychiatry. 2011 May;82(5):476-86; Rohrer JD and Warren JD, Curr Opin Neurol 24:542–549). Some cases of FTLD with Tau-negative, ubiquitin positive inclusions may not demonstrate any TDP43 immunoreactivity and FUS can be the pathological protein (associated with FUS mutations; van Langenhove T, van der Zee J, van

Broeckhoven C. The molecular basis of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum. Ann Med. 2012 PMID: 22420316). Finally, there are cases of ubiquitin-positive FTLD without TDP43 and FUS immunoreactivity and some of these can be associated with CHMP2B mutations (Seelaar H, Rohrer JD, Pijnenburg YAL, et al. J Neurol Neurosurg Psychiatry. 2011 May;82(5):476-86).

A number of metabolic genetic conditions can also present as young onset dementia. The majority of these demonstrate autosomal recessive, X-linked, or mitochondrial inheritance and ascertainment of a family history of consanguinity or marriage within a genetically homogeneous group, such as Ashkenazi Jews. These diseases are relatively rare, but accurate diagnosis will allow proper genetic counseling and provide prognostic guidance to the family, which is an integral component in the management of dementia. These include disorders of amino acids and organic acids metabolism, lysosomal storage diseases, leukodystrophies, mitochondrial diseases, and disorders of metal metabolism. While many of these genetic metabolic diseases are multi-system disorders, most will also suffer a significant degree of cognitive impairment (Hsiung 2008). In some cases, such as Neimann-Pick Type C, dementia can be the main and only clinical presentation. A selected list of metabolic disorders that can present with progressive dementia in the young is listed in Table 2.

Table 2: Some metabolic causes of dementia and the genetic mutations associated with them

Amino Acids Metabolism	**Chromosome**	**Enzyme Deficiency**	**Diagnostic Tests**
Propionic Acidemia (PCCA,& PCCB)	(13q32, & 3q21-q22)	Propionyl-CoA carboxylase	deficient activity of propionyl-CoA carboxylase, ketotic hyperglycinemia
Lysosomal Storage Disorders			
Fabry Disease	Xq22	α-galactosidase A	deficient α-galactosidase A activity in leukocytes & elevated urinary

			oligosaccharides (trihexoside) assay
Gaucher Disease	1q21	Glucocerebrosidase	Deficient glucocerebrosidase activity in leukocytes
Niemann-Pick type C	18q11 & 14q24.3	NPC1 & NPC2	Skin fibroblast assay for intracellular cholesterol accumulation (filipin staining) or gene mutation analysis
Adult-onset Tay Sach's disease (GM2 gangliosidoses)	15q24.1	Hexosaminidase A	Hexosaminidase A levels; HEXA mutation screening
Unknown			
Kufs Disease	unknown		Tissue biopsy demonstrating ceroid lipofuscin
Leukodystrophies			
Adrenoleukodystrophy	Xq28	ATP-binding cassette (ABC) transporter, subfamily D, Type 1	Elevated level of very long-chain fatty acids in leukocytes or fibroblasts
Metachromatic leukodystrophy	22.q13.31-qter & 10q22.1	Aryl-sulfatase A, or saposin B	Leukocyte arylsulfatase A assay; Urine for elevated sulfatides
Krabbe disease (globoid cell leukodystrophy)	14q31	galactocerebroside β-galactosidase	Leukocyte galactocerebroside β-galactosidase
Mitochondrial Disorders			
e.g. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) & Myoclonus epilepsy with ragged-red fibers (MERRF)	Mitochondrial DNA;	Mitochondrial transfer RNA gene mutations (mtDNA tRNA)	EEG; Serum and CSF lactate, mtDNA mutation analysis; muscle biopsy
POLG related syndromes	15q25	DNA polymerase subunit gamma-1 (POLG)	Identification of POLG mutations
Metal Metabolism			
Pantothenate kinase-associated neurodegeneration (Previously Hallervorden-Spatz Disease)	20p13-p12.3	PKAN2	Mutation analysis of the PKAN2 gene; MRI pallidal abnormalities with decreased T2 signal intensity, compatible with iron deposits ('eye of the tiger' sign)

Comment [SEB1]: No Mention of CADASIL

Wilson disease	13q14.3	ATPase, Cu(2+)-transporting beta polypeptide, ATP7B	Serum ceruloplasmin, urinary copper

In addition to genetic based neurodegenerative diseases, other systemic diseases can also lead to progressive cognitive decline that mimics early onset dementia. Some reviews such as that of Fadil et al, 2009, list as many as 61 causes of early onset dementias. For example, infectious diseases such as HIV and syphilis, autoimmune inflammatory diseases such as lupus with CNS involvement, and paraneoplastic syndromes with limbic encephalitis, can all lead to progressive cognitive impairment. (Table 3) Since the differential diagnosis is wide, a structured and systematic approach is needed to ensure all potentially reversible conditions have been ruled out. The clinical presentation must be carefully assessed to fully understand the cognitive profile involved. Dementia secondary to a systemic disease more commonly lead to a "subcortical dementia" due to injury to the white matter pathways and damage to the basal ganglia structures with psychomotor slowing, frontal dysexecutive syndrome, and memory retrieval difficulties, whereas "cortical dementia" is generally characterized by problems in specific cognitive domains (e.g. Alzheimer disease with episodic memory impairment, or progressive non-fluent aphasia with speech / language abnormalities) with relative preservation of processing speed.

High quality neuroimaging (MRI) and cerebral spinal fluid analysis is recommended in all patients with early onset dementia to rule out structural, inflammatory, and infectious diseases. A full neurological and general physical examination is also needed to look for evidence of involvement in other organ systems. A tailored investigation will be required depending on the suspected etiology. (Table 3)

Table 3: Some systemic diseases that may lead to progressive cognitive impairment and dementia

Systems	**Examples**	**Associated Symptoms (may or may not be present)**	**Diagnostic Tests**
CNS Vascular Disease	Primary CNS Vasculitis	Headaches, Focal Neurological Deficits	MRI; CSF analysis; biopsy
	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)	Migraine-like headaches; focal neurological deficits and seizures	MRI; genetic analysis for NOTCH3 gene mutation
Infection	HIV associated neurocognitive disorders	Variable, constitutional symptoms, with or without opportunistic infections	HIV screen; Plasma HIV viral load; CD4
	Neurosyphilis	Tabes dorsalis	Serum RPR; MHA-TP; CSF VDRL
	Whipple's disease	Gastrointestinal symptoms, weight loss, and polyarthralgia; Oculomasticatory and Oculofacial-skeletal myorhythmia in only 20%, but highly specific	Duodenal biopsy showing granular foamy macrophages with PAS-positive inclusions; CSF PCR for *Tropheryma Whipplei*
Neoplastic	Primary CNS Lymphoma	Headaches; Focal Neurological Deficits	CSF analysis; Brain/ meningeal biopsy
Autoimmune	Hashimoto encephalitis	Thyroid abnormalities	Anti-microsomal Ab; Anti-thyroglobulin Ab
	Limbic encephalitis	Cancer (Breast, Lung, testicular, teratoma colon, gyneocological)	Anti-Hu, Anti-Ri, Anti-Yo, Anti-Ma1, Anti-Ma2, Anti-VGKC, Anti-CV2, Anti-amphiphysin, Anti-NMDAR, Anti-AMPAR, Anti-GAD Antibodies
	Lupus with CNS involvement	Multiple organ systems	ANA; ENA; CSF analysis; MRI
Endocrine and Nutritional	Hypothyroidism	Fatigue, weight gain	TSH; free T4
	B12 deficiency	Fatigue, Macrocytic anemia	B12
	Porphyria	Seizures, personality	Blood, urine, and stool

		change, abdominal pain, skin lesions	porphyrins analysis

Common issues with early onset dementias

In the literature, the following issues are raised as common to the various causes of early onset dementias:

1. delay in recognizing the neurological cause of behavioral symptoms (such as encountered in the behavioural variant of FTD, Neary et al, 2005) or visual-perceptual impairment (such as the posterior cortical atrophy variant of AD, Crutch et al, 2012), causing visits to different physicians and more expensive workups than in later onset dementias.
2. Early symptoms are most often considered a 'psychological'issue rather than a neurologic one, resulting in patients being diagnosed with depression, going through burnout or mid-life crisis. Physicians are unaware of the symptoms and signs in early-onset dementia and therefore misdiagnosis often occurs (van Vliet et al, 2011).
3. need to refer to genetic counseling and testing (Fortea et al, 2011)
4. different social impact than later onset dementias since many are still at work, often have young families and there is higher caregiver burden (Bentham & La Fontaine, 2005; Hunt, 2011)
5. although there is less co-morbidity than in later onset dementias, there is more heterogeneity in causes of early onset dementias and less concordance between clinical phenotype and underlying pathology (Snowden et al, 2011)

Considerations for the CCCDTD

1. because of the rarity of early onset dementias, specialized tertiary centers with access to genetic counseling and other diagnostic resources should be identified across Canada, in order to facilitate referral of appropriate subjects.
   (Grade 1)

2. because of the rarity of early onset dementias, a registry should be established for interested asymptomatic carriers of genes leading to early onset dementias, in order to facilitate access to therapeutic studies and obtain accurate prevalence estimate of these conditions (only one, CJD, has compulsory reporting).
   (Grade 1)
3. training of health professionals from Canada and abroad interested in early onset dementias should be facilitated by access to these specialized clinics
   (Grade 1)
4. genetic counselors should be funded and have major roles in dealing with these patients and families
   (Grade 1)

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