Dementia

Md Moshiur Rahman , Syeda Neyamot-e-Ferdousi and Forhad H. Chowdhury

Abstract: Approximately 47.5 million people are dementia sufferers worldwide. Dementia is a frequent etiology of morbidity and mortality with the growing elderly population. This translates to a vast global economic impact. Risk factors of dementia include oxidative stress, infection, the accumulation of excessive protein deposits in the cerebrum, metal accumulation, and cholinesterase disorders. The bulk of dementias affecting the elderly population are due to Alzheimer's disease, Lewy body dementia, ischemic brain injury, and normal pressure hydrocephalus (NPH). Among the long list of etiologies of dementia, only a few are reversible and treatable. Among the treatable causes, NPH-induced dementia is surgically treatable. In this chapter, avery short discussion and differentiation of common causes of dementia are provided. Surgical management of NPH is discussed in the later part of the chapter.

Abbreviations

AD	Alzheimer's disease	BOLD	blood-oxygen-level-dependent
CSF	cerebrospinal fluid	CT	computerized tomography
BLB	dementia with Lewy bodies	ETV	endoscopic third ventriculostomy
FTD	frontotemporal dementia	fMRI	functional MRI
ICP	intracranial pressure	iNPH	idiopathic normal pressure hydrocephalus
LBs	Lewy bodies	LP	Lumboperitoneal
MRI	magnetic resonance imaging	NFT	neurofibrillary tangle
NPH	normal-pressure hydrocephalus	PD	Parkinson's disease
ROS	reactive oxygen species	VaD	vascular dementia
VP	ventriculoperitoneal	VA	ventriculo-atrial

1. Introduction

The word dementia comes from the Latin demens ("de": private; "mens": intellect, knowledge), referring to the cognitive deterioration of these functions. Dementia is primarily a severe, persistent, and permanent neurological impairment syndrome, a subtype of which is Alzheimer's disease. Acute-onset degenerative dementia has relatively few causes. The word "reversible dementia" is frequently utilized to characterize reversible encephalopathies but is rather inaccurate owing to the connotations correlated with the phrase "dementia". Irreversible, non-progressive cognitive dysfunction describes static encephalopathy, such as that correlated with severe brain damage, stroke, or sensitivity to neurotoxins. Practically, the differentiation between dementia with reversible encephalopathy requires evidence of reversibility via correct therapy of the causative disease. The bulk of dementias affecting the elderly population are due to Alzheimer's disease (approximately 60%), Lewy body dementia (nearly 15%), and ischemic brain injury (nearly 15%), while the other cases of encephalopathy are caused by a vast variety of etiologies.

2. Dementia and Causes

The American Psychiatric Association described dementia as any mental disability or global cognitive loss in an earlier intact individual, marked by the degradation of cognitive, social, emotional, and behavioral capacities, sufficiently extreme to negatively impact on sufferers' everyday lives (American Psychiatric Association 2013). Approximately 47.5 million people are dementia sufferers worldwide (Hügel and Jackson 2015). Hence, dementia has become a frequent etiology of morbidity and mortality with the growing elderly population (Fadil et al. 2009). This translates to a vast global economic impact (Wimo et al. 2013). Risk factors of dementia include oxidative stress, infection, the accumulation of excessive protein deposits in the cerebrum, metal accumulation, and cholinesterase disorders (Choi et al. 2012).

Three primary etiologies of dementia are Alzheimer's disease (AD), vascular dementia (VaD), and dementia with Lewy bodies (DLB). Vascular dementia is due to blockage from a blood clot of one or more cerebral blood vessels. When a large blood artery in the brain is obstructed, it is considered a stroke. However, the most common events that contribute to vascular dementia are a sequence of minor arterial blockages that go undiagnosed for years before manifesting as dementia.

Taking an antiplatelet drug on a daily basis is an effective stroke prevention therapy for those who have acquired atherosclerosis.

About half of the elderly adults with dementia are reported to have neurological signs of more than one etiology of dementia. Mixed dementia, AD, and VaD are frequently encountered together. Depression, thyroid disease, the adverse effects of some drugs, alcohol misuse, vitamin deficiencies, and other factors might induce dementia-like symptoms (not dementia).

Dementia is a syndrome defined as a gradual and irreversible pathological process characterized by a degenerative pathology that causes degeneration and neuronal death in several cerebral regions, causing the brain's function and structure to decline. Furthermore, it is primarily a later-life disorder that is not associated with the natural aging process (Vemuri et al. 2011). DLB, mixed dementia with AD, VaD, Parkinson's disease (PD), Creutzfeldt–Jakob disease, frontotemporal dementia, Huntington's disease, normal hydrocephalus pressure (NPH), and progressive supranuclear palsy are the most common kinds of dementia (de Villemeur 2013; Picascia et al. 2016; Eddy et al. 2016; Reed et al. 2003; Cunningham et al. 2015) (Tables 1 and 2).

Nondegenerative dementia can be due to a variety of causes, including infections, head injuries, brain tumors, subdural hematomas, and clear and spontaneous hydrocephalus strain (Ghosh 2010). Age, sex hormones (Barron and Pike 2012), genetic variables (Chou et al. 2017; Jamal et al. 2017; Kanatsu and Tomita 2017; Loy et al. 2014), and external conditions (chemical exposures and metals) (Uchoa et al. 2016) are all risk factors that might promote dementia. The molecular basis of dementia, neuronal death, and synaptic damage is unknown, and it may differ according to the type of neurodegenerative disorder. However, common characteristics of dementia include the involvement of certain common causes, such as oxidative stress, neuroinflammation, and irregular protein folding (Finkel and Holbrook 2000; Santos et al. 2014; Polidori and Scholtes 2016; Rahal et al. 2014; Chen et al. 2016; Stefaniak and O'Brien 2016; Barrientos et al. 2015; Craig-Schapiro et al. 2010; Shimizu et al. 2011).

Table 1. Chronic degenerative dementias.

Alzheimer's disease
Lewy body dementia
Frontotemporal dementia
Progressive supranuclear palsy
Parkinson's disease
Multiple system atrophy
Corticobasalganglionic degeneration
Huntington's disease
Multiple sclerosis
Mitochondrial disorders
Amyotrophic lateral sclerosis

Source: Authors' compilation based on data from de Villemeur (2013); Picascia et al. (2016); Eddy et al. (2016); Reed et al. (2003); Cunningham et al. (2015).

Table 2. Acute dementias.

Traumatic brain injury
Creutzfeldt–Jakob disease
Neurotoxin exposure
Vascular dementia
Reversible encephalopathies
Infectious disease

Source: Authors' compilation based on data from de Villemeur (2013); Picascia et al. (2016); Eddy et al. (2016); Reed et al. (2003); Cunningham et al. (2015).

3. Diagnosing Dementia

Dementia is diagnosed using mini-mental state examination (MMSE) (Chapter 2; Section 1).

3.1. Molecular Neuroimaging of the Dementias

3.1.1. Identification of Abnormal Characters of Cerebral Function Utilizing Molecular Neuroimaging

Irregular trends in dementias can show new insights into how these diseases interrupt brain circuits. They can also be useful when diagnosing differentials. Irregular findings usually include a decreased metabolism or

blood supply in different brain areas affected by the disorder and vice versa in some other situations. Molecular neuroimaging was also used to determine abnormal cerebral function patterns in people who are asymptomatic but carry genetic potential factors for dementia.

3.1.2. Physiological Basis of Functional MRI in Dementia

The most widely used fMRI method to classify cortical functions depends on contrast scanning of the interior blood-oxygen-level-dependent (BOLD) signal. The MRI signal during one cognitive state is usually equated to a monitoring task or a responsive standard condition in fMRI investigations. The BOLD fMRI signal, as well as neurovascular coupling, which links cellular functions to hemodynamic alterations, is predicted to vary in healthy aging and during neurodegenerative dementia pathological processes. Changes in cerebral fMRI activation patterns between controls and persons with neurodegenerative dementia could be due to disease-related neuropathological abnormalities as well as variations in fMRI-measured neurovascular coupling. When taken together, BOLD-based fMRI provides a novel and readily accessible method for studying intact human cognition as well as improvements in neural activity associated with stable aging and neurodegenerative-disease-related dysfunctions (Logothetis et al. 2001; Shmuel et al. 2006; Kwong et al. 1992; Ogawa et al. 1992; Buckner et al. 2005; Cavanna and Trimble 2006; D'Esposito et al. 2003; Iadecola 2004).

3.2. Memory Dysfunction in Dementia

3.2.1. Episodic Memory

Episodic memory is a declarative memory device that is utilized to recall a specific event in one's life, such as a date with a friend. Episodic memory is primely characterized by what people with an injured medial temporal lobe cannot recall compared to normal people. The basal forebrain with Broca's medial septum and lateral bands, the presubiculum, the retrosplenial cortex, the fornix, the mammillothalamic tract, and the anterior thalamus nucleus are all important components of the episodic memory network (Mesulam 2000). A lesion in either of these systems may induce the disorder characteristic of episodic memory system dysfunction. Episodic memory loss develops slowly and gradually in degenerative conditions such AD, frontotemporal dementia, and DLB (Solomon and Budson 2003). Episodic memory often deteriorates over time in disorders involving several brain areas, such as vascular dementia and multiple sclerosis. Tumors, medicines, hypoglycemia, traumatic brain injury, and Korsakoff's syndrome are all linked to memory loss. In Azheimer's illness, the hippocampus and amygdala, as well as the parietal, temporal, and frontal lobes, are predisposition sites for pathogenic involvement. Since the hippocampus and other medial temporal lobe anatomical structures are the first and most seriously impacted cerebral areas in AD, episodic memory—particularly, the file cabinet elements of episodic memory—is the first and most severely damaged cognitive function. Telling the same stories, asking the same questions, missing appointments, and leaving the stove on are all common symptoms. Another feature of the disease's episodic memory impairment is that memory is harmed even when many rehearsals maximize information learning or encoding and retrieval demands are reduced with the utilization of a multiple-choice recognition test. "Fast rate of forgetting" is a term used to describe this type of memory loss. Besides fast forgetting, Alzheimer's disease patients often suffer memory disturbances and mistaken memories. Patients with such delusions may believe they have already turned off the burner or taken their medicines, causing them to neglect certain tasks. A hallucination or a delusion can be confused with a false memory. For example, a dementia patient may claim to see and communicate with a long-dead family member. Both AD and moderate cognitive dysfunction are linked to the frontal lobes, but not as much as the medial temporal lobes (Dickerson and Sperling 2009; Schonknecht et al. 2009). Memory distortions and fabricated memories may be caused by frontal lobe impairment in AD. People with AD, on the other hand, have a substantial pathology in the parietal cortex, which can manifest early in the treatment process (McKee et al. 2006).

3.2.2. Semantic Memory

Semantic memory is our storage of factual and conceptual knowledge that is unrelated to any particular memory, for example, the color of a ripe mango or the purpose of a glass. Semantic memory is a declarative and explicit memory system, similar to episodic memory (Schacter et al. 2000). Semiconductor memory is preserved in patients with severe episodic memory loss, such as destruction of the Papez circuit or surgical displacement of the medial temporal lobes (Corkin 1984). In its general sense, semantic memory comprises all of our global

information and is unrelated to episodic memory. As a result, it is possible that semantic memory dwells in numerous cortical regions of the brain. Visual pictures are preserved in nearby visual association zones, according to evidence (Vaidya et al. 2002). Semantic memory is located in the inferolateral temporal lobes, primarily on the left, according to a more restricted interpretation supported by the naming and classification tests by which it is normally tested (Damasio et al. 1996; Perani et al. 1999).

The most frequent clinical illness that disrupts semantic memory is Alzheimer's disease (Price and Morris 1999; Greene and Hodges 1996). TBI, stroke, surgical injuries, encephalitis, and tumors are among the conditions that can impact the temporal lobes infero-laterally and induce functional memory (semantic memory) loss. All semantic memory tests, such as single-word interpretation, naming, and visual intelligence, are impaired in patients with semantic dementia. When semantic memory impairment is suspected, the assessment should contain the same elements as an episodic memory disorder work-up.

3.2.3. Procedural Memory

The capacity to learn unconscious cognitive and behavioral abilities and algorithms is referred to as procedural memory. Procedural memory is implicit and non-declarative. Driving a car with a normal transmission or learning to play the violin are two examples. The procedural memory system is clearly separate from the episodic memory system since it is spared in cases with significant episodic memory disorders. Procedural-memory-involving areas are the motor cortex, basal ganglia, and cerebellum (Daselaar et al. 2003; Exner et al. 2002). In Alzheimer's disease, the cerebellum and basal ganglia are relatively excluded. In spite of episodic memory loss, these cases show consistent development and preservation of procedural memory skills (Baird and Samson 2009). Because PD is the most prevalent disorder that disrupts procedural memory, Lewy body dementia is the most common neurodegenerative disorder that disrupts procedural memory. Patients with Huntington's disease with olivopontocerebellar degeneration in the preliminary stages of the disease have reduced procedural memory, while performing relatively normally on episodic memory tests (Heindel et al. 1989; Salmon et al. 1998). Strokes, tumors, and hemorrhages can all affect procedural memory by causing injury to the cerebellum or basal ganglia. Patients with significant depression have trouble with procedural memory tests, which could be due to basal ganglia dysfunction. Analysis of procedural memory disorders is akin to that of episodic memory disorders; management relies on the process of the specific disease. Finally, patients whose episodic memory was harmed by a static disease, such as cerebral encephalitis, were able to rehabilitate successfully by utilizing procedural memory to acquire new skills (Glisky and Schacter 1989).

3.2.4. Working Memory

Concentration, classic fields of attention, short-term memory, and working memory relate to the capability to transiently maintain and utilize necessary data. Working memory is a declarative and explicit form of memory. The working memory has generally been split into three parts: one for processing phonological information, another for processing spatial information, and an executive system for allocating attention resources (Baddeley 1998). Working memory is composed of a network of subcortical and cortical units that alter based on the task (Rowe et al. 2000). The prefrontal cortex is engaged in practically every working memory task (Fletcher and Henson 2001). Subsequent brain regions are commonly linked to prefrontal areas to complete a circuit in the cortical and subcortical area network. More areas on the right cerebral hemisphere are involved in spatial working memory, while more areas on the left side are involved in phonological working memory.

Patients with AD, PD, Huntington's disease, DLB, and less-prevalent illnesses including progressive supranuclear palsy may have problems with working memory (Calderon et al. 2001). Strokes, tumors, multiple sclerosis, head injuries, and other conditions can all affect working memory. Almost every type of aphasia can affect phonological working memory since it entails silent rehearsal of spoken material. Hyperactivity disorder, obsessive compulsive disorder, insomnia, and schizophrenia are among the attention-deficit disorders that can interfere with memory performance (Egeland et al. 2003; Klingberg et al. 2002). Working memory disorders can manifest in a variety of ways, including failure to concentrate or difficulty doing a new job with multiple steps. Working memory impairments are assessed in the same way episodic memory abnormalities are. The treatment is determined by the underlying cause.

3.3. The Neuropathology of the Dementing Disorders

3.3.1. Dementia with Lewy Bodies (DLB)

Lewy body dementia is a frequent neurodegenerative etiology of dementia following AD. Okazaki and colleagues (Okazaki et al. 1961) were the first to describe DLB in 1961. Significant quantities of intracytoplasmic inclusions resembling Lewy bodies (LBs) were demonstrated in the cerebral cortex (Kuzuhara et al. 1988; Spillantini et al. 1998). LBs are found in transentorhinal and entorhinal cortex, cingulate gyrus, amygdala, frontotemporal cortex, and insular cortex in DLB, as well as the brainstem, diencephalic regions, and basal forebrain in PD (McKee et al. 1998). The combination of LB pathology and Alzheimer's pathology, as well as neurochemical abnormalities and neuronal loss, in DLB is likely to cause dementia (McKee et al. 1998; Samuel et al. 1996; Apaydin et al. 2002). DLB is frequently associated with AD, and some researchers have classified it as a subset of the disease (Kosaka et al. 1984). DLB, on the other hand, is part of a spectrum of LB diseases, with PD on one end and DLB on the other. Cortical LBs are circumscribed inclusions in the deeper layers of the cortex that are found in medium- to small-sized pyramidal neurons of the cortex. Cortical LBs have a similar ultrastructure to brainstem LBs, but the fibrils are less densely oriented and there is no core to identify (Nussbaum and Polymeropoulos 1997).

3.3.2. Progressive Supranuclear Palsy

Progressive supranuclear palsy macroscopic traits include globus pallidus atrophy, subthalamic hippocampus, and midbrain and pontine tegmentum. Microscopically, tau immune-reactive neurofibrillary tangles, neuropil loops, tufted astrocytes, and inclusions of oligodendroglia occur. Tau abnormalities have been identified in the subcortical parenchyma and neocortex, entorhinal cortex, striatum, globus pallidus, hippocampus, substantia nigra, third nerve nuclei, red nuclei, pontine nuclei, cerebellar dentate nuclei, inferior olives, and spinal cord dorsal horns.

3.3.3. Neurofibrillary Tangle Dementia

The macroscopic pathology of dementia of neurofibrillary tangles frequently demonstrates extensive brain atrophy. The condition is marked by extensive neurofibrillary tangles (NFTs), neuropil threads, and ghost tangles in the hippocampus, entorhinal cortex, transentorhinal, and amygdala, with only infrequent engagement of other neocortical areas.

3.3.4. Vascular Dementia (VaD)

The presence of VaD in autopsy studies differs widely, ranging from 2% to 58% (Barclay et al. 1985; Esiri 2000). Vascular dementia can predominate in older age groups over some other causes of dementia. The heterogeneity of vascular dementia, which frequently coexists with other degenerative pathologies, makes estimating its prevalence difficult (Nolan et al. 1998). When microvascular abnormalities like white matter lesions and amyloid angiopathy are involved, approximately all AD cases have some degree of vascular disease (Kalaria 2000). Much clinical research investigating the relationship between AD and cerebrovascular damage has proved the pathology of large arteries, such as infarctions and hemorrhages, as well as large amounts of small vessel lesions, such as gaps lacunes (Bowling and Beal 1995; Skoog et al. 1993; Snowden et al. 2007). Microvascular disease has been identified as a major cause of dementia in older people (Kalaria et al. 1993; Kövari et al. 2007; Sonnen et al. 2007; White et al. 2002).

Strategic Infarct Dementia

Focal ischemic lesions, which typically consist of small- to medium-sized infarcts in clinically significant brain areas like the anterior cerebral artery area, the dominant angular gyrus, longitudinal hippocampus, unilateral to longitudinal medial thalamus, prevalent caudate nucleus, and basal forebrain, can also occur in dementia syndrome in conjunction with certain influential neurological impairments (Jellinger 2007).

3.3.5. Normal-Pressure Hydrocephalus (NPH)

NPH, also known as hydrocephalus of mal-resorption, is a type of communicating hydrocephalus where the ventricles have an excess of cerebrospinal fluid (CSF) and the cerebrospinal fluid pressure is normal or slightly higher. As the CSF volume builds up in the ventricles, the intracranial pressure inside the skull rises, crushing

surrounding brain tissue and causing neurological issues. Dementia, urinary incontinence, and gait abnormalities are the characteristic trinity of symptoms of the condition. Hakim and Adams were the first to demonstrate the condition in 1965 (Adams et al. 1965). NPH is frequently misinterpreted as PD or AD (due to gait and cognitive dysfunction).

Epidemiology

Primary NPH comprises most of the cases. The prevalence of NPH rises with age, and the majority of patients are over 60. It is calculated that it affects less than 1% of people under the age of 65 and up to 3% of those over the age of 65. There is no difference in the occurrence in males and females (Younger 2005; Brean and Eide 2008; Tanaka et al. 2009). The prevalence of NPH is defined to be between 2 and 6% among dementia patients.

Signs and Symptoms

NPH presents a characteristic trilogy of clinical symptoms (called the Hakim's triad or Adam's triad). Gait deviation, dementia, and urinary incontinence make up the trio (usually referred to as "weird walking water" or "wet, wacky, and wobbly").

Approximately all patients have gait abnormalities, which are frequently the first sign. The corticospinal tract motor fibers are impinged on by the swelling of the lateral ventricles. The usual gait impairment in NPH is a wide-based, sluggish, narrow-stepped, "stuck to the floor", or "magnetic" movement. The abnormal gait seen in NPH is similar to those seen in PD. The gait disturbance can be minor, noticeable, or severe: "marked" means the patient has trouble walking due to significant instability; "severe" means the patient is unable to walk without assistance (Krauss et al. 2001; Ropper and Samuels 2009).

Dementia manifests itself as progressive cognitive abnormalities in 60% of cases at the time of treatment. Distortions in the frontal lobe and subcortex are mostly responsible for this (Younger 2005). Planning, organization, focus, and concentration are among the first shortcomings. Taking medications, managing finances, keeping track of appointments, driving, daytime sleeping, short-term memory difficulties, and psychomotor slowness are among the other weaknesses. Late-stage traits include indifference, slowed thinking, less drive, and reduced communication.

Urinary incontinence develops later and affects 50% of cases at the time of management. Urinary dysfunction starts with frequent urination, particularly at night, that escalates to urge incontinence and persistent incontinence (Younger 2005).

In idiopathic NPH (iNPH), apathy is the most frequent behavioral abnormality and it contributes to gait abnormalities. Oropharyngeal dysphagia "falling spells" as well as impulsive, violent conduct, both verbal and physical, are other uncommon signs. Oropharyngeal dysphagia is caused by ventricular dilatation compressing the corticobulbar tract (Allali et al. 2016).

Pathogenesis

Although the exact etiology is uncertain, there is agreement on several processes:

- An imbalance presents between CSF production versus resorption.
- CSF outflow resistance is frequently high.

Over-secretion of CSF or restriction of CSF flow in the ventricles do not cause the condition NPH and should be differentiated from hydrocephalus ex vacuo, which occurs due to brain atrophy (Figure 1).

The primary (sometimes known as idiopathic) and secondary causes of the condition are frequently distinguished. The fundamental cause of main NPH has yet to be discovered (Figure 2). Primary NPH affects adults aged 40 and up, with the elderly being the most commonly affected.

Secondary NPH can afflict people of any age and can be caused by things like subarachnoid hemorrhage, brain surgery (Figure 3), meningitis, traumatic brain injury, or brain radiation.

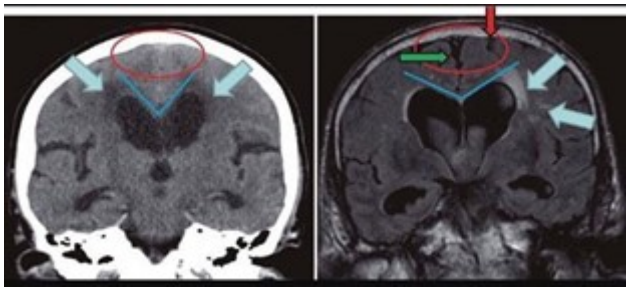

Figure 1. CT scan of head: coronal views. Left image: NPH. Right image: brain atrophy (hydrocephalus ex vacuo). Blue lines are indicating callosal angle. In the red circle, sulci are shown which are prominent in brain atrophy. Source: Figure by authors.

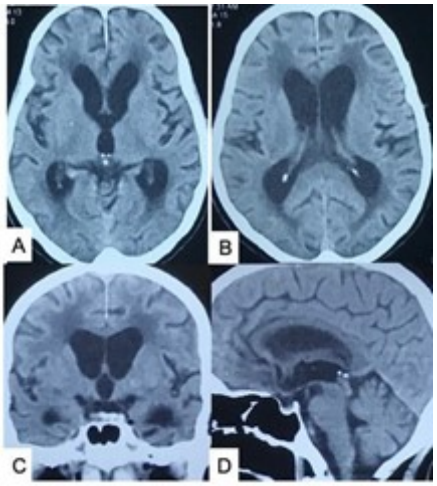

Figure 2. CT scan of head. (**A**,**B**) Axial section, (**C**) coronal, and (**D**) sagittal section showing iNPH. Source: Figure by authors.

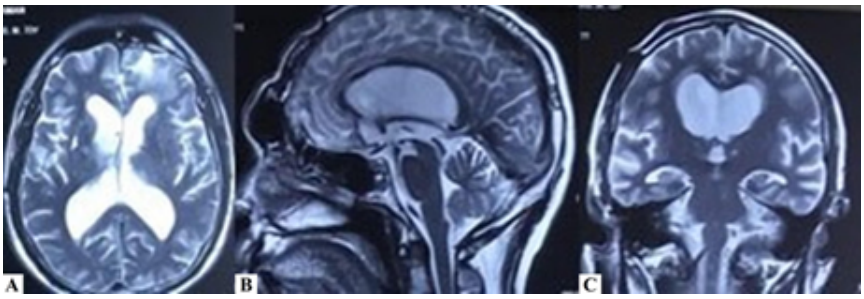

Figure 3. MRI of brain T2W images. (**A**) axial, (**B**) sagittal, and (**C**) coronal showing secondary NPH developed after removal of left frontal meningioma. Source: Figure by authors.

Diagnosis

Along with ventricular enlargement on neuroimaging, cases with suspicion of NPH should have characteristic symptoms. The following are the internationally accepted, evidence-based diagnostic criteria for iNPH:

1: Gradual beginning after 40 years of age, symptoms lasting 03–06 months, clinical evidence of balance or gait impairment, cognitive impairment, or urine incontinence.

2: To show larger ventricles as well as no macroscopic blockage to CSF flow, imaging from MRI or CT scans is required. On imaging, at least one of the temporal horns of the lateral ventricles should be enlarged, with impingement against the falx cerebri at a callosal angle of 90° on the coronal image, indicating changes in brain water content or normal CSF flow (also known as "flow void") at the cerebral aqueduct and fourth ventricle.

MRI scans are the best option. It is difficult to tell the difference between normal and increased ventricular size due to cerebral atrophy. Up to 80% of patients are unidentified and mistreated due to the complexity of diagnosis. Imaging should also demonstrate the lack of any pathology or blockages in the brain. Despite the fact that all NPH cases have enlarged ventricles, not all elderly cases with enlarged ventricles have iNPH.

Hydrocephalus ex vacuo is the medical term for enlarged ventricles caused by cerebral atrophy (Figure 1).

Before deciding on a CSF diversion treatment, the iNPH concordance neuroimaging findings as well as clinical improvement after clinical tests are critical.

Current data of imaging utilized:

1. Evans' index;
2. Magnetic resonance elastography;
3. Callosal angles;
4. Glymphatic MRI;
5. Reversed aqueductal CSF net flow;
6. The SILVER Index: subarachnoid space is enlarged disproportionately;
7. Computerized volumetric assessment of the cranial CSF distribution;
8. Hyperdynamic CSF motion;
9. MRI water apparent diffusion coefficient;
10. Computed tomography perfusion;
11. Arterial spin labeling perfusion MRI;
12. Brain to ventricle ratios at the posterior and anterior commissure levels and three-dimensional (3D) volumetric convexity cistern to ventricle ratios;
13. High-field 3D-MRI study of subarachnoid space (Liew et al. 2019).

The Miller Fisher test is performed with 30–50 mL of CSF removed. To evaluate for symptoms of symptomatic improvement, cognitive function and gait are often examined soon before and within 2–3 h following the LP. The Miller Fisher test is similar to the CSF infusion test or the lumbar test. These tests have a positive predictive value of more than 90% but a negative predictive value of under 50%. CSF pressure should be normal or slightly elevated on the LP. Normal glucose levels, cell contents, and protein levels should all be present in CSF (Marmarou et al. 2005, 2007; Tarnaris et al. 2009).

Treatment

CSF diversion is the first-line treatment for suspected cases of NPH. Shunt surgery has proven to be the only long-lasting and effective treatment for iNPH (Vanneste et al. 1992). The current ideal treatment is the insertion of a ventriculoperitoneal (VP) shunt (Poca et al. 2004).

Kuriyama et al. conducted a statewide, hospital-based study in Japan and found that among patients diagnosed with iNPH the lumboperitoneal (LP) shunt was the top choice (55.1%), followed by the VP shunt (43.2%) (Kuriyama et al. 2017).

In iNPH patients, a modification of the VP shunt that placed the peritoneal end between two epiploic layers of the larger omentum resulted in a satisfactory outcome with no major postoperative problems (Grigorean et al. 2017).

Tudor et al. observed no changes in outcomes (balance, cognitive, function, mobility, and gait) between endoscopic third ventriculostomy (ETV) and normal therapy (VP shunting with a nonprogrammable valve) for iNPH cases in a systematic review (Tudor et al. 2015).

Bayar et al. investigated the efficacy of LP shunt surgery in NPH patients, finding that headache was cured in nearly all cases by the third month, and urinary incontinence, gait disturbance, and cognitive functions were recovered in 72%, 86%, and 65% of cases at the end of the first year, respectively (Bayar et al. 2018).

In a prospective multicenter trial, the efficacy and safety of LP shunts for cases with iNPH were investigated, with the previously completed VP shunt cohort study serving as a historical control group. The authors finally commented that the efficacy and safety of LP shunts with programmable valves for the management of patients with iNPH are comparable to those of VP shunts. Shunt revisions were, however, more common in LP shunt cases than in VP shunt cases (Miyajima et al. 2016). In research, only approximately 40% of iNPH cases improved following shunt operation, and only about 60% indicated their general health state was better than preoperatively using the self-assessed modified Rankin Scale (smRS) (Andrén et al. 2018). Vascular comorbidities, such as hypertension, stroke, diabetes, and cardiac disease, had no effect on the iNPH patients' early outcomes after shunt surgery. Cases with a history of stroke and hypertension, on the other hand, had a less favorable outcome,

according to the same study. Surgery for NPH is clearly superior to the natural course or conservative treatment, according to risk–benefit studies (Liew et al. 2019).

Outcome

Eighty-five percent of patients see improvements in their gait. When surgery is performed early in the illness course, approximately 80% of patients' cognitive problems improve. Incontinence recovers in up to 80% of patients, but only in 50–60% of those who had a shunt inserted late in the illness course. Patients with mere gait deviation, mild or no autonomic incontinence, and mild dementia are the most likely to improve. Shunt failure, shunt obstruction, infections such as ventriculitis, under- or over-drainage, and the formation of a subdural hematoma are all risks associated with shunt implantation (Molde et al. 2017; Allali et al. 2017; Jo et al. 2017).

Medication

There are no drugs that can help with iNPH. Acetazolamide and other diuretics are only indicated for use in cases who are not candidates for shunt implantation.

Author Contributions: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, M.M.R. and S.N.-e.-F.; writing—review and editing, visualization, supervision, F.H.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

Adams, R. D., C. M. Fisher, S. Hakim, R. G. Ojemann, and W. H. Sweet. 1965. Symptomatic Occult Hydrocephalus with Normal Cerebrospinal-Fluid Pressure. *The New England Journal of Medicine* 273: 117–26. [CrossRef] [PubMed]

Allali, Gilles, Magali Laidet, Stéphane Armand, Arnaud Saj, Paul Krack, and Frédéric Assal. 2017. Apathy and higher level of gait control in normal pressure hydrocephalus. *International Journal Psychophysiology* 119: 127–31. [CrossRef] [PubMed]

Allali, Gilles, Valentina Garibotto, and Frèdèric Assal. 2016. Parkinsonism differentiates idiopathic normal pressure hydrocephalus from its mimics. *Journal of Alzheimer's Disease* 54: 123–27. [CrossRef] [PubMed]

American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American psychiatric publishing.

Andrén, Kerstin, Carsten Wikkelsö, Nina Sundström, Simon Agerskov, Hanna Israelsson, Katarina Laurell, Per Hellström, and Mats Tullberg. 2018. Long-term effects of complications and vascular comorbidity in idiopathic normal pressure hydrocephalus: A quality registry study. *Journal of Neurology* 265: 178–86. [CrossRef] [PubMed]

Apaydin, Hulya, J. Eric Ahlskog, Joseph E. Parisi, Bradley F. Boeve, and Dennis W. Dickson. 2002. Parkinson disease neuropathology, later-developing dementia and loss of the levodopa response. *Archives of Neurology* 59: 102–12. [CrossRef]

Baddeley, Alan. 1998. Recent developments in working memory. *Current Opinion in Neurobiology* 8: 234–38. [CrossRef]

Baird, Amee, and Séverine Samson. 2009. Memory for music in Alzheimer's disease: Unforgettable? *Neuropsychology Reviews* 19: 85–101. [CrossRef]

Barclay, Laurie L., Alexander Zemcov, John P. Blass, and Fletcher H. McDowell. 1985. Factors associated with duration of survival in Alzheimer's disease. *Biological Psychiatry* 20: 86–93. [CrossRef]

Barrientos, Ruth M., Meagan M. Kitt, Linda R. Watkins, and Steven F. Maier. 2015. Neuroinflammation in the normal aging hippocampus. *Neuroscience* 309: 1–15. [CrossRef]

Barron, Anna M., and Christian J. Pike. 2012. Sex hormones, aging, and Alzheimer's disease. *Frontiers in Bioscience (Elite Edition)* 4: 976–97. [CrossRef]

Bayar, Mehmet Akif, Ayhan Tekiner, Haydar Celik, Ali Yilmaz, Guner Menekse, Timur Yildirim, Fatih Alagoz, Yahya Guvenc, and Yavuz Erdem. 2018. Efficacy of Lumboperitoneal Shunting in Patients with Normal Pressure Hydrocephalus. *Turkish Neurosurgery* 28: 62–66. [CrossRef] [PubMed]

Bowling, Allen C., and M. Flint Beal. 1995. Bioenergetic and oxidative stress in neurodegenerative diseases. *Life Sciences* 56: 1151–71. [CrossRef] [PubMed]

Brean, Are, and Per K. Eide. 2008. Prevalence of probable idiopathic normal pressure hydrocephalus in a Norwegian population. *Acta Neurologica Scandinavica* 118: 48–53. [CrossRef] [PubMed]

Buckner, Randy L., Abraham Z. Snyder, Benjamin J. Shannon, Gina LaRossa, Rimmon Sachs, Anthony F. Fotenos, Yvette I. Sheline, William E. Klunk, Chester A. Mathis, John C. Morris, and et al. 2005. Molecular, structural, and functional characterization of Alzheimer's disease: Evidence for a relationship between default activity, amyloid, and memory. *Journal of Neuroscience* 25: 7709–17. [CrossRef] [PubMed]

Calderon, J., R. J. Perr, S. W. Erzinclioglu, G. E. Berrios, T. R. Dening, and John R. Hodges. 2001. Perception, attention, and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 70: 157–64. [CrossRef]

Cavanna, Andrea E., and Michael R. Trimble. 2006. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* 129: 564–83. [CrossRef]

Chen, Wei-Wei, X. I. A. Zhang, and Wen-Juan Huang. 2016. Role of neuroinflammation in neurodegenerative diseases. *Molecular Medicine Reports* 13: 3391–96. [CrossRef]

Choi, Dong-Young, Young-Jung Lee, Jin Tae Hong, and Hwa-Jeong Lee. 2012. Antioxidant properties of natural polyphenols and their therapeutic. Potentials for Alzheimer's disease. *Brain Research Bulletin* 87: 144–53. [CrossRef]

Chou, Ping-Song, Meng-Ni Wu, Mei-Chuan Chou, I. Chien, and Yuan-Han Yang. 2017. Angiotensin-converting enzyme insertion/deletion polymorphism and the longitudinal progression of Alzheimer's disease. *Geriatrics & Gerontology International* 17: 1544–50. [CrossRef]

Corkin, Suzanne. 1984. Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H.M. *Seminars in Neurology* 4: 249–59. [CrossRef]

Craig-Schapiro, Rebecca, Richard J. Perrin, Catherine M. Roe, Chengjie Xiong, Deborah Carter, Nigel J. Cairns, Mark A. Mintun, Elaine R. Peskind, Ge Li, Douglas R. Galasko, and et al. 2010. YKL-40: A novel prognostic fluid biomarker for preclinical Alzheimer's disease. *Biological Psychiatry* 68: 903–12. [CrossRef] [PubMed]

Cunningham, E. L., B. McGuinness, B. Herron, and A. P. Passmore. 2015. Dementia. *Ulster Medical Journal* 84: 79–87. [PubMed]

Damasio, Hanna, Thomas J. Grabowski, Daniel Tranel, Richard D. Hichwa, and Antonio R. Damasio. 1996. A neural basis for lexical retrieval. *Nature* 380: 499–505. [CrossRef] [PubMed]

Daselaar, Sander M., Serge A. R. B. Rombouts, Dick J. Veltman, Jeroen G. W. Raaijmakers, and Cees Jonker. 2003. Similar network activated by young and old adults during the acquisition of a motor sequence. *Neurobiology of Aging* 24: 1013–19. [CrossRef] [PubMed]

D'Esposito, Mark, Leon Y. Deouell, and Adam Gazzaley. 2003. Alterations in the BOLD fMRI signal with aging and disease: A challenge for neuroimaging. *Nature Reviews Neuroscience* 4: 863–72. [CrossRef]

de Villemeur, Thierry Billette. 2013. Creutzfeldt-Jakob disease. *Handbook of Clinical Neurology* 112: 1191–93. [CrossRef]

Dickerson, Bradford C., and Reisa A. Sperling. 2009. Large—Scale functional brain network abnormalities in Alzheimer's disease: Insights from functional neuroimaging. *Behavioral Neurology* 21: 63–75. [CrossRef]

Eddy, Clare M., Ellice G. Parkinson, and Hugh E. Rickards. 2016. Changes in mental state and behaviour in Huntington's disease. *The Lancet Psychiatry* 3: 1079–86. [CrossRef]

Egeland, Jens, Kjetil Sundet, Bjorn Rishovd Rund, Arve Asbjornsen, Kenneth Hugdahl, Nils Inge Landro, Anders Lund, Atle Roness, and Kirsten I. Stordal. 2003. Sensitivity and specificity of memory dysfunction in schizophrenia: A comparison with major depression. *Journal of Clinical and Experimental Neuropsychology* 25: 79–93. [CrossRef]

Esiri, Margaret M. 2000. Which vascular lesions are of importance in vascular dementia? *Annals of the New York Academy of Sciences* 903: 239–43. [CrossRef]

Exner, Cornelia, Janka Koschack, and Eva Irle. 2002. The differential role of premotor frontal cortex and basal ganglia in motor sequence learning: Evidence from focal basal ganglia lesions. *Learning & Memory* 9: 376–86.

Fadil, Halim, Aimee Borazanci, Elhachmia Ait Ben Haddou, Mohamed Yahyaoui, Elena Korniychuk, Stephen L. Jaffe, and Alireza Minagar. 2009. Early onset dementia. *International Review of Neurobiology* 84: 245–62. [CrossRef] [PubMed]

Finkel, Toren, and Nikki J. Holbrook. 2000. Oxidants, oxidative stress, and the biology of aging. *Nature* 408: 239–47. [CrossRef] [PubMed]

Fletcher, Paul C., and R. N. A. Henson. 2001. Frontal lobes and human memory: Insights from functional neuroimaging. *Brain* 124: 849–81. [CrossRef] [PubMed]

Ghosh, Amitabha. 2010. Endocrine, metabolic, nutritional, and toxic disorders leading to dementia. *Annals of Indian Academy of Neurology* 13: S63–S68. [CrossRef]

Glisky, Elizabeth L., and Daniel L. Schacter. 1989. Extending the limits of complex learning in organic amnesia: Computer training in a vocation domain. *Neuropsychologia* 27: 173–78. [CrossRef]

Greene, John D. W., and John R. Hodges. 1996. Identification of famous faces and famous names in early Alzheimer's disease. Relationship to anterograde episodic and general semantic memory. *Brain* 119: 111–28. [CrossRef]

Grigorean, Valentin Titus, Aurelia Mihaela Sandu, Mihai Popescu, Ioan Stefan Florian, Cristian Dumitru Lupascu, and Corina Lupascu Ursulescu. 2017. Our initial experience with ventriculo-epiplooic shunt in treatment of hydrocephalus in two centers. *Neurologia i Neurochirurgia Polska* 51: 290–98. [CrossRef]

Heindel, William C., David P. Salmon, Clifford W. Shults, Patricia A. Walicke, and Nelson Butters. 1989. Neuropsychological evidence for multiple implicit memory systems: A comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *Journal of Neuroscience* 9: 582–87. [CrossRef]

Hügel, Helmut M., and Neale Jackson. 2015. Polyphenols for the prevention and treatment of dementia diseases. *Neural Regeneration Research* 10: 1756–58. [CrossRef]

Iadecola, Costantino. 2004. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature Reviews Neuroscience* 5: 347–60. [CrossRef] [PubMed]

Jamal, Salma, Sukriti Goyal, Asheesh Shanker, and Abhinav Grover. 2017. Computational Screening and Exploration of Disease-Associated Genes in Alzheimer's Disease. *Journal of Cellular Biochemistry* 118: 1471–79. [CrossRef] [PubMed]

Jellinger, Kurt A. 2007. The enigma of vascular cognitive disorder and vascular dementia. *Acta Neuropathologica* 113: 349–88. [CrossRef] [PubMed]

Jo, Kwang Wook, Youngkook Kim, Geun-Young Park, Ik Seong Park, Yongjun Jang, Sohn Dong Gyun, and Sun Im. 2017. Oropharyngeal dysphagia in secondary normal pressure hydrocephalus due to corticobulbar tract compression: Cases series and review of literature. *Acta Neurochirurgica* 159: 1005–11. [CrossRef]

Kalaria, Raj N. 2000. The role of cerebral ischemia in Alzheimer's disease. *Neurobiology of Aging* 21: 321–30. [CrossRef]

Kalaria, R. N., S. U. Bhatti, W. D. Lust, and G. Perry. 1993. The amyloid precursor protein in ischemic brain injury and chronic hypoperfusion. *Annals of the New York Academy of Sciences* 695: 190–93. [CrossRef]

Kanatsu, Kunihiko, and Taisuke Tomita. 2017. Molecular mechanisms of the genetic risk factors in pathogenesis of Alzheimer disease. *Frontiers in Bioscience* 22: 180–92.

Klingberg, Torkel, Hans Forssberg, and Helena Westerberg. 2002. Training of working memory in children with ADHD. *Journal of Clinical and Experimental Neuropsychology* 24: 781–91. [CrossRef]

Kosaka, K., M. Yoshimura, K. Ikeda, and H. Budka. 1984. Diffuse type of Lewy body disease, progressive dementia with abundant cortical Lewy bodies and senile changes of varying degree—A new disease? *Clinical Neuropathology* 3: 185–92.

Kövari, E., Gabriel Gold, F. R. Herrmann, Alessandra Canuto, P. R. Hof, Constantin Bouras, and Panteleimon Giannakopoulos. 2007. Cortical microinfarcts and demyelination affect cognition in cases at high risk for dementia. *Neurology* 68: 927–31. [CrossRef]

Krauss, Joachim K., Michael Faist, Martin Schubert, Jan J. Borremans, Carl H. Lücking, and Wiltrud Berger. 2001. Evaluation of Gait in Normal Pressure Hydrocephalus Before and After Shunting. In *Advances in Neurology, Volume 87: Gait Disorders*. Edited by Evzen Ruzicka, Mark Hallett and Joseph Jankovic. Philadelphia: Lippincott Williams & Wilkins, pp. 301–9.

Kuriyama, Nagato, Masakazu Miyajima, Madoka Nakajima, Michiko Kurosawa, Wakaba Fukushima, Yoshiyuki Watanabe, Etsuko Ozaki, Yoshio Hirota, Akiko Tamakoshi, Etsuro Mori, and et al. 2017. Nationwide hospital-based survey of idiopathic normal pressure hydrocephalus in Japan: Epidemiological and clinical characteristics. *Brain and Behavior* 7: e00635. [CrossRef] [PubMed]

Kuzuhara, S., H. Mori, N. Izumiyama, M. Yoshimura, and Y. Ihara. 1988. Lewy bodies are ubiquitinated. A light and electron microscopic immunocytochemical study. *Acta Neuropathologica* 75: 345–53. [CrossRef] [PubMed]

Kwong, Kenneth K., John W. Belliveau, David A. Chesler, Inna E. Goldberg, Robert M. Weisskoff, Brigitte P. Poncelet, David N. Kennedy, Bernice E. Hoppel, Mark S. Cohen, and Robert Turner. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences* 89: 5675–79. [CrossRef] [PubMed]

Liew, Boon, Kiyoshi Takagi, Yoko Kato, Shyam Duvuru, Sengottuvel Thanapal, and Balamurugan Mangaleswaran. 2019. Current updates on idiopathic normal pressure hydrocephalus. *Asian journal of Neurosurgery* 14: 648–56. [CrossRef] [PubMed]

Logothetis, Nikos K., Jon Pauls, Mark Augath, Torsten Trinath, and Axel Oeltermann. 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412: 150–57. [CrossRef]

Loy, Clement T., Peter R. Schofield, Anne M. Turner, and John B. J. Kwok. 2014. Genetics of dementia. *The Lancet* 383: 828–40. [CrossRef]

Marmarou, Anthony, Harold F. Young, and Gunes A. Aygok. 2007. Estimated incidence of normal pressure hydrocephalus and shunt outcome in patients residing in assisted-living and extended-care facilities. *Neurosurgical Focus* 22: E1. [CrossRef]

Marmarou, Anthony, Marvin Bergsneider, Petra Klinge, Norman Relkin, and Peter McL Black. 2005. The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. *Neurosurgery* 57: S17–S28. [CrossRef]

McKee, A. C., N. W. Kawall, J. S. Schumacher, and M. Flint Beal. 1998. The neurotoxicity of amyloid beta protein in aged primates. *Amyloid* 5: 1–9. [CrossRef]

McKee, Ann C., Rhoda Au, Howard J. Cabral, Neil W. Kowall, Sudha Seshadri, Caroline A. Kubilus, Jon Drake, and Philip A. Wolf. 2006. Visual association pathology in preclinical Alzheimer disease. *Journal of Neuropathology & Experimental Neurology* 65: 621–30. [CrossRef]

Mesulam, M. Marsel. 2000. *Principles of Behavioral and Cognitive Neurology*. New York: Oxford University Press.

Miyajima, Masakazu, Hiroaki Kazui, Etsuro Mori, and Masatsune Ishikawa. 2016. One-year outcome in patients with idiopathic normal-pressure hydrocephalus: Comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. *Journal of Neurosurgery* 125: 1483–92. [CrossRef] [PubMed]

Molde, Karin, Lars Söderström, and Katarina Laurell. 2017. Parkinsonian symptoms in normal pressure hydrocephalus: A population-based study. *Journal of Neurology* 264: 2141–48. [CrossRef] [PubMed]

Nolan, Karen A., M. Maddelena Lino, Arthur W. Seligmann, and John P. Blass. 1998. Absence of vascular dementia in an autopsy series from a dementia clinic. *Journal of the American Geriatrics Society* 46: 597–604. [CrossRef] [PubMed]

Nussbaum, R., and M. Polymeropoulos. 1997. Genetics of Parkinson's disease. 1997. Genetics of Parkinson's disease. *Human Molecular Genetics* 6: 1687–91. [CrossRef] [PubMed]

Ogawa, Seiji, David W. Tank, Ravi Menon, Jutta M. Ellermann, Seong G. Kim, Helmut Merkle, and Kamil Ugurbil. 1992. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America* 89: 5951–55. [CrossRef] [PubMed]

Okazaki, Haruo, Lewis E. Lipkin, and Stanley M. Aronson. 1961. Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion. *Journal of Neuropathology and Experimental Neurology* 20: 237–44. [CrossRef]

Perani, Daniela, Stefano F. Cappa, Tatiana Schnur, Marco Tettamanti, Simona Collina, Màrio Miguel Rosa, and Ferruccio Fazio. 1999. The neural correlates of verb and noun processing. A PET study. *Brain* 122: 2337–44. [CrossRef]

Picascia, Marta, Brigida Minafra, Roberta Zangaglia, Luciana Gracardi, Nicolo Gabriele Pozzi, Elena Sinforiani, and Claudio Pacchetti. 2016. Spectrum of cognitive disorders in idiopathic normal pressure hydrocephalus. *Functional Neurology* 31: 143–47. [CrossRef]

Poca, Maria A., Maria Mataró, Maria Del Mar Matarín, Fuat Arikan, Carmen Junqué, and Juan Sahuquillo. 2004. Is the placement of shunts in patients with idiopathic normal-pressure hydrocephalus worth the risk? Results of a study based on continuous monitoring of intracranial pressure. *Journal of Neurosurgery* 100: 855–66. [CrossRef]

Polidori, M. Cristina, and Marlies Scholtes. 2016. Beyond and behind the fingerprints of oxidative stress in age-related diseases: Secrets of successful aging. *Archives of Biochemistry and Biophysics* 595: 50–53. [CrossRef]

Price, Joseph L., and John C. Morris. 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer s disease. *Annals of Neurology* 45: 358–68. [CrossRef] [PubMed]

Rahal, Anu, Amit Kumar, Vivek Singh, Brijesh Yadav, Ruchi Tiwari, Sandip Chakraborty, and Kuldeep Dhama. 2014. Oxidative stress, prooxidants, and antioxidants: The interplay. *BioMed Research International* 63: 187–94. [CrossRef] [PubMed]

Reed, Laurence J., Dan Lasserson, Paul Marsden, Nicola Stanhope, Tom Stevens, Fernando Bello, Derek Kingsley, Alan Colchester, and Michael D. Kopelman. 2003. FDG-PET findings in the Wernicke-Korsakoff syndrome. *Cortex* 39: 1027–45. [CrossRef] [PubMed]

Ropper, Allan H., and Martin A. Samuels. 2009. *Adams and Victor's Principles of Neurology*. New York: McGraw-Hill Medical.

Rowe, James B., Ivan Toni, Oliver Josephs, Richard S. J. Frackowiak, and Richard E. Passingham. 2000. The prefrontal cortex: Response selection or maintenance within working memory? *Science* 288: 1656–60. [CrossRef] [PubMed]

Salmon, David P., Tara T. Lineweaver, and William C. Heindel. 1998. Nondeclarative memory in neurodegenerative disease. In *Memory in Neurodegenerative Disease: Biological, Cognitive, and Clinical Perspectives*. Edited by Alexander I. Troster. Cambridge: Cambridge University Press, pp. 210–25.

Samuel, William, Douglas Galasko, Eliezer Masliah, and Lawrence A. Hansen. 1996. Neocortical Lewy body counts correlate with dementia in the Lewy body variant of Alzheimer's disease. *Journal of Neuropathology and Experimental Neurology* 55: 44–52. [CrossRef]

Santos, Jose R., Auderlan M. Gois, Deise M. F. Mendonça, and Marco A. M. Freire. 2014. Nutritional status, oxidative stress, and dementia: The role of selenium in Alzheimer's disease. *Frontiers in Aging Neuroscience* 6: 206. [CrossRef]

Schacter, Daniel L., Anthony D. Wagner, and Randy L. Buckner. 2000. Memory systems of 1999. In *The Oxford Handbook of Memory*. Edited by Endel Tulving and Fergus I. M. Craik. New York: Oxford University Press, pp. 627–43.

Schonknecht, Oskar Dieter Peter, Aoife Hunt, Pablo Toro, Marcus Henze, Uwe Haberkorn, and Johannes Schröder. 2009. Neural correlates of delayed episodic memory in patients with mild cognitive impairment—A FDG PET study. *Neuroscience Letters* 467: 100–4. [CrossRef]

Shimizu, Motohiro, Joji Ishikawa, Yuichirou Yano, Satoshi Hoshide, Kazuyuki Shimada, and Kazuomi Kario. 2011. The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. *Atherosclerosis* 219: 316–21. [CrossRef]

Shmuel, Amir, Mark Augath, Axel Oeltermann, and Nikos K. Logothetis. 2006. Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nature Neuroscience* 9: 569–77. [CrossRef]

Skoog, Ingmar, Lars Nilsson, Bo Palmertz, Lars-Arne Andreasson, and Alvar Svanborg. 1993. A population-based study of dementia in 85-year-olds. *New England Journal of Medicine* 328: 153–58. [CrossRef]

Snowden, Julie, David Neary, and David Mann. 2007. Frontotemporal lobar degeneration: Clinical and pathological relationships. *Acta Neuropathologica* 114: 31–38. [CrossRef] [PubMed]

Solomon, P. R., and A. E. Budson. 2003. Alzheimer's disease. *Clinical Symposia* 54: 1–44.

Sonnen, Joshua A., Eric B. Larson, Paul K. Crane, Sebastien Haneuse, Ge Li, Gerald D. Schellenberg, Suzanne Craft, James B. Leverenz, and Thomas J. Montine. 2007. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Annals of Neurology* 62: 406–13. [CrossRef] [PubMed]

Spillantini, Maria Grazia, R. Anthony Crowther, Ross Jakes, Masato Hasegawa, and Michel Goedert. 1998. Alpha-Synuclein in fi lamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proceedings of the National Academy of Sciences of the United States of America* 95: 6469–73. [CrossRef] [PubMed]

Stefaniak, James, and John O'Brien. 2016. Imaging of neuroinflammation in dementia: A review. *Journal of Neurology, Neurosurgery & Psychiatry* 87: 21–28. [CrossRef]

Tanaka, Naofumi, Satoshi Yamaguchi, Hiroyasu Ishikawa, Hiroshi Ishii, and Kenichi Meguro. 2009. Prevalence of possible idiopathic normal-pressure hydrocephalus in Japan: The Osaki-Tajiri project. *Neuroepidemiology* 32: 171–75. [CrossRef]

Tarnaris, Andrew, Ahmed K. Toma, Neil D. Kitchen, and Laurence D. Watkins. 2009. Ongoing search for diagnostic biomarkers in idiopathic normal pressure hydrocephalus. *Biomarkers in Medicine* 3: 787–805. [CrossRef]

Tudor, Katarina Ivana, Mario Tudor, Jenny McCleery, and Josip Car. 2015. Endoscopic third ventriculostomy (ETV) for idiopathic normal pressure hydrocephalus (iNPH). *Cochrane Database of Systematic Reviews* 7: CD010033. [CrossRef]

Uchoa, Mariana F., V. Alexandra Moser, and Christian J. Pike. 2016. Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors. *Frontiers in Neuroendocrinology* 43: 60–82. [CrossRef]

Vaidya, Chandan J., Margaret Zhao, John E. Desmond, and John D. E. Gabrieli. 2002. Evidence for cortical encoding specificity in episodic memory: Memory—Induced reactivation of picture processing areas. *Neuropsychologia* 40: 2136–43. [CrossRef]

Vanneste, Jeroen, Paul Augustijn, Clemens Dirven, Wee Fu Tan, and Zeger D. Goedhart. 1992. Shunting normal-pressure hydrocephalus: Do the benefits outweigh the risks? A multicenter study and literature review. *Neurology* 42: 54–59. [CrossRef] [PubMed]

Vemuri, Prashanthi, Gyorgy Simon, Kejal Kantarci, Jennifer L. Whitwell, Matthew L. Senjem, Scott A. Przybelski, Jeffrey L. Gunter, Keith A. Josephs, David S. Knopman, Bradley F. Boeve, and et al. 2011. Antemortem differential diagnosis of dementia pathology using structural MRI: Differential-STAND. *Neuroimage* 55: 522–31. [CrossRef] [PubMed]

White, L. O. N., Helen Petrovitch, John Hardman, James Nelson, Daron G. Davis, G. Webster Ross, Kamal Masaki, Lenore Launer, and William R. Markesbery. 2002. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. *Annals of the New York Academy of Sciences* 977: 9–23. [CrossRef] [PubMed]

Wimo, Anders, Linus Jönsson, John Bond, Martin Prince, Bengt Winblad, and Alzheimer Disease International. 2013. The worldwide economic impact of dementia 2010. *Alzheimer's & Dementia* 9: 1–11. [CrossRef]

Younger, David S. 2005. Adult Normal Pressure Hydrocephalus. In *Motor Disorders*. Edited by David S. Younger. Philadelphia: Lippincott Williams & Wilkins, pp. 581–84.