Atypical and potentially reversible types of dementia and cognitive dysfunctions: Normal Pressure Hydrocephalus

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Normal Pressure Hydrocephalus

Content

1. Definition
2. Etiology
3. Symptomatology
4. Diagnosis / Differential Diagnosis
5. Treatment
6. Case Report
7. Discussion
Detective
- crime!
- motive?

Physician
- symptom!
- disease?

ΙΠΠΟΚΡΑΤΗΣ
(Hippocrates)
Normal Pressure Hydrocephalus (NPH) - general

**past:** uncritical indications, immature technology of valves, low therapeutic success, high complication rate.

**present:** moderate diagnostic and therapeutic procedures, clinical improvement rates 70-90%, operative therapy superior in comparison to conservative or natural course.

Without therapy NPH leads within a few months to deterioration of clinical findings and without surgery decreases the quality of life.

Today only 10-20% of the patients with an iNPH receive a specialized and professional therapy.

Normal pressure hydrocephalus (NPH) is often unrecognized.

*Kiefer & Unterberg 2012*
Epidemiology

• Although NPH is known for more than 40 years epidemiological studies are rare.

• Prevalence is estimated at 0.1% among individuals aged ≥ 60 years.

• 6% of nursing home residents may have NPH. *(Bejjani et al., 2005)*

- Meta-analyses from 1988 and 2003: 1% - 1.6% of dementia attributed to NPH. *(Clarfield, 1988; Clarfield, 2003)*

- Experts suggest: NPH 5% of dementia population. *(Vanneste, 2000)*

- Denmark study: 4% of patients referred for dementia were diagnosed with NPH. *(Bech-Azeddine et al., 2001)*
Epidemiology

• Frequency doubles with each decade of life thereafter (Overview at Brean et al., 2008).

• Although NPH is considered a syndrome associated with older adults, up to one quarter of patients are under 50 years of age.

• Prevalence in males is higher than in females (Meyer et al., 2004).

• 75% of patients with iNPH also have cerebrovascular dementia or Alzheimer‘s disease.

• Studies have shown that 40% to 75% of patients with iNPH have beta-amyloid or other typical histological findings of Alzheimer‘s disease, while 60% have signs of a cerebrovascular disease. (overview in: Kiefer & Unterberg 2012)
Definition

The Special Clinical Problem of Symptomatic Hydrocephalus with Normal Cerebrospinal Fluid Pressure

Observations on Cerebrospinal Fluid Hydrodynamics

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*J. neurol. Sci.* (1965) 2: 307–327

• The condition was first described 1964 by the colombian neurosurgeon Hakim and colleagues.

• In the context of NPH they observed a ventricular dilatation and normal cerebrospinal fluid (CSF) pressure during lumbar puncture.

(Hakim & Adams, 1965; Adams et al., 1965)
**Definition**

• The fully developed syndrome is characterized by a specific symptom-triad:

  1. **Progressive cognitive decline / dementia** ([subcortical dementia]) -100%-

  2. **Gait difficulties** - ~90% -

  3. **Urinary incontinence** - 45-90% -

  (Mamarou et al., 2005)

• **Progressive ventriculomegaly**, without mechanical obstruction, in the face of normal mean intracranial and intraventricular pressure.

  (Levine, 2008; Bergschneider et al., 2006)
Normal CSF Flow

- CSF is formed by the choroid plexus in the ventricles producing approximately 20 to 30 ml per hour.
- CSF circulates from two lateral to a single midline third ventricle into the fourth ventricle.
- CSF exits the ventricular system (through the foramina of Magendie and Luschkae) and passes into the subarachnoidal space.
- Most of the CSF is absorbed into the arachnoid villi.

(Verrees & Selman, 2004; Byrd, 2006; Hickey, 2003; Wilson & Williams, 2006)
Etiology

• NPH can be:
  
  • **Idiopathic** (ca. 2/3 of patients) or
  
  • **Secondary** (ca. 1/3 of patients) to a multitude of insults (e.g. subarachnoid hemorrhage, meningitis, encephalitis, head trauma).

  • NPH may develop years after the original injury!

  • Despite intensive research, idiopathic NPH is still a mysterious entity of unclear etiology.

*(Bradley et al., 2004; Krauss & Halve, 2004)*
Idiopathic NPH - Etiology

Theories on etiology of NPH:

- Defective absorption of CSF (Bateman, 2000)
- Deep white matter ischemia (Bradley et al., 1991)
- Redistribution of vascular pulsations and decreased elasticity (compliance) of the brain parenchyma, vessels and subarachnoid spaces (Bateman, 2009)

(overview see Chrysikopoulos, 2009)
Pathophysiology

- The imbalance of CSF production and resorption is not caused by an increased CSF production.

- Cause of the disease seems to be a limitation of the Windkessel effect (pressure reservoir function) of the basal cerebral arteries. As a result of that higher shear and compressive forces occur in the brain parenchyma. Because of physiological and physical differences mainly the periventricular brain tissue gets damaged and reduced in volume. Through these focal brain damage results a ventricular dilatation.

- Another consequence is a decreased cerebral blood flow (high coincidence of iNPH with disorders of cerebral circulation). Through that lower CSF-turnover and lower clearance of toxic metabolics (coincidence of iNPH with Morbus Alzheimer).

*Kiefer & Unterberg 2012*
Etiology

- Whatever the etiology, the result is a dilatation of the ventricles (ventriculomegaly). That implies a communicating hydrocephalus, where the arachnoid villi are unable to reabsorb CSF sufficiently without an obstruction to CSF flow in the ventricular system.

- The progressive ventriculomegaly may cause compression of structures adjacent to the ventricles, resulting in the clinical manifestations of the disease.
  - e.g. pressure on the frontal lobes: dementia symptoms
  - e.g. pressure on cortical center for bladder control: incontinence
  - e.g. pressure on corticospinal fibers lateral to ventricles: gait disturbance

(Hickey, 2003; Bejjani & Hammer, 2005)
Diagnosis - clinical features

**Gait disturbance** (up to 92%):
- Slow, broad based and short-stepped gait
- Shortened stride length, broad „magnetic“ gait (feet „sticking“ to the floor)
- Balance disturbance
- Difficulties in turning on the body’s long axis
- Relative less movement of the arms

Lemke & Meier 2010
Diagnosis – clinical features and neuropsychological testing

**Dementia** (almost everyone):
Type: subcortical dementia
- lack of drive
- psychomotor slowing
- reduced attention and concentration performance
- affective indifference
- memory impairment (esp. of immediate and delayed recall [verbal memory], but in comparison to Alzheimer’s disease with better recognition performance)
- apathy with loss of agility, spontaneity and communication
- anxiety and depression

Duinkerke et al., 2004; Thomas et al., 2005; Iddon et al., 1999
Diagnosis - clinical features

**Urinary incontinence (ca. 43%):**
- Urgent incontinence

Detrusor hyperactivity with partial or total absence of central inhibitory control

The urinary incontinence is not expressed by the early dementia but by a neurogenic bladder dysfunction as an autonomic syndrome. In addition, the gait disturbance complicates a fast way to the toilet.

In later stages a frontal lobe syndrome disables the awareness of the desire to urinate.

*Kiefer & Unterberg 2012*
Diagnostics – cerebral imaging (cCT / cMRI):
Resorption disturbance of the CSF with:
- **Ventricular enlargement** out of proportion to sulcal atrophy.
- Rounding of the frontal horns.
- **Disproportion** between the **enlarged inner** and rather **narrow outer CSF spaces**
- **Narrowed CSF spaces over the convexity** near the **vertex**
- **Periventricular hypodensities** (diffusion of CSF) in cCT and hyperdensity in T2-cMRI
- Only low to moderate general brain atrophy or/and moderate vascular pathology which does not explain the clinical symptoms.
Diagnostics – cerebral imaging (cCT / cMRI):

Kiefer & Unterberg, Differentialdiagnose und Therapie des Normaldruckhydrozephalus, Deutsches Ärzteblatt, Jg. 109, Heft 1-2, 9. Januar 2012
Diagnosis - Drainage of the CSF

The CSF tap test

- Removal of approximately **30 to 70 mL of CSF** via lumbar puncture.
- The test is simple to perform, wide spread, but however, controlled studies are rare.
- The single removal of CSF simulates a shunt-effect in advance.
- The test considered **positive** if the symptoms (esp. gait disturbance) temporarily **improve** after the removal of CSF and is - in addition to the **clinical symptoms** and the **cerebral imaging** – the **most essential criterion** for the diagnosis of NPH.

Diagnosis - Drainage of the CSF (tap test)

- Assessment of gait improvement by measuring the time and distance
- The test should be considered positive when walking time or walking distance improve at least 20-30% and/or the cognitive performance improve at least 10%. (Kiefer & Unterberg 2012)
- Sensitivity of the CSF tap test 26-61% (Marmarou et al. 2005).
- Repeat of the test useful in unclear results (Gupta & Lang 2011).

Other technique:
- External continuous lumbar drainage.

(Paulus et al. In: Diener & Weimar 2012)
Therapy

Implantation of a ventriculoperitoneal (VP) shunt
(alternative: ventriculoatrial or ventriculopleural shunt).

Success of the surgery in studies approx. 70-90%.

Prognosis:
Better than dementia in Alzheimer’s disease
(Improvement after shunt-implantation: gait disturbance> urinary incontinence> dementia)

Alternatively:
Conservative therapy by intermittent therapeutic CSF-drainage in medical inoperable patients.


(Bergsneider et al., 2005)
Complications (today <20%, earlier 35-40%):
- Overshunting may result in ventricular collapse,
  causing a subdural hematoma.
- Undershunting may not have optimal improvement of the symptoms.
- Shunt infections
- Symptomatic epilepsy
- Acute or chronic subdural hematoma
- Shunt dysfunction

Therapy - predictors

Predictors for positive results after shunt implantation:
- Gait disturbance clinically predominant
- Gait disturbance before cognitive decline
- Short history esp. of the cognitive impairment
- Mild to moderate cognitive deficits
- Low to moderate lesions of the brain tissue in the MRI
- Significant improvement after lumbar CSF-drainage

Predictors for negative results after shunt implantation:
- Severe dementia
- Cortical dementia
- Pronounced cortical atrophy
- Pronounced vascular leukencephalopathy

Diagnosis

- Diagnosis of NPH is difficult because of the symptomatological similarities with other neurological problems, such as Alzheimer’s disease and Parkinson’s disease.
- Because of the difficult diagnosis of NPH a diagnostical process comprising clinical signs and symptoms, radiographic findings and confirmatory testing is recommended.

(Byrd, 2006)
Differential diagnosis (dementia)

- **Cortical dementia**
  - Alzheimer’s dementia
  - Frontotemporal Dementia
- **Subcortikal dementia**
  - Lewy-Body-Dementia
  - Idiopathich und vascular Parkinson-syndrome
  - Progressive supranuclear Paralysis (PSP)
  - Aids-Dementia-Complex
  - Depression in elderly (“pseudodementia”)
- **Mixed dementia**
  - Vascular Dementia

*Kiefer & Unterberg 2012*
## Differential diagnosis

### NPH Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Manifestation</th>
<th>Comparison to NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>• Cognitive impairments characterized by aphasia, apraxia, and agnosia</td>
<td>• Cognitive impairment characterized by slowness of thought, inattentiveness, and apathy</td>
</tr>
<tr>
<td></td>
<td>• Gait impairment usually not a predominant feature</td>
<td>• Gait impairment is usually the first and most pronounced feature</td>
</tr>
<tr>
<td></td>
<td>• Urinary incontinence may appear in later stages</td>
<td>• Urinary urgency/incontinence may occur later</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>• Gait impairment is usually narrow-based, shuffling, with bradykinesia, decreased arm swing, and stooped posture</td>
<td>• Gait impairment usually more wide-based; bradykinesia, decreased arm swing, and stooped posture not as apparent</td>
</tr>
<tr>
<td></td>
<td>• Dementia symptoms may appear later in the disease</td>
<td>• Symptoms usually will not improve with levodopa medications</td>
</tr>
<tr>
<td></td>
<td>• Includes resting tremors, rigidity, masked face, and hypophonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Symptoms will improve with levodopa medications</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia (stroke, multi-infarct dementia, vertebrobasilar insufficiency)</td>
<td>• Usually presents with focal neurologic deficits attributable to a specific area of cerebral damage</td>
<td>• CT/MRI will show evidence of infarct(s)</td>
</tr>
<tr>
<td></td>
<td>• Gait disturbance may be due to motor weakness or limb ataxia</td>
<td>• Will not usually present with the classic clinical triad of NPH</td>
</tr>
</tbody>
</table>

*(Fig. Differential Diagnosis in: Byrd, 2006)*
### Differential diagnosis - Dementia

<table>
<thead>
<tr>
<th>Comparison of dementia characteristics</th>
<th>Alzheimer’s disease</th>
<th>Vascular dementia</th>
<th>Normal pressure hydrocephalus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory impairment</td>
<td>X</td>
<td>X</td>
<td>Impaired retrieval</td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Impaired visuospatial process</td>
<td>X</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>Impaired language</td>
<td>X</td>
<td>X^a</td>
<td>Bradyphrenia</td>
</tr>
<tr>
<td>Impaired complex motor skills</td>
<td>X</td>
<td>X^a</td>
<td></td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Impaired attentiveness</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

^a Can occur based on location of infarction.

(Table in: Factora & Luciano, 2006, page 648)
Differential diagnosis (gait disturbance)

- Peripheral neuropathy
- Spinal stenosis
- Inner ear damage
- Chronic alcoholism
- Vitamine-B6- and -B12-deficiency
Differential diagnosis

General results unlikely for idiopathic normal pressure hydrocephalus:

- intracranial pressure > 25 cm H2O
- Age < 40 years
- Asymmetric or only temporal findings
- Cortical deficits e.g. aphasia, apraxia, paresis
- Progressive dementia without gait disturbance and without ventriculomegaly

Kiefer & Unterberg 2012
NPH & Alzheimer

Patients with **moderate-to-severe tau and Ab pathology** demonstrated **more severe baseline impairment** on a composite measure of cognition and **poorer performance** postoperatively on NPH symptom severity scales and measures of cognition. Finally, in sharp contrast to individuals with less severe pathology, patients with **moderate-to-severe pathology failed to demonstrated benefit** on any study measures accessing gait, cognition, and incontinence at 4-month follow up.

_Hamilton et al., 2010:_
Summary

- Normal Pressure Hydrocephalus (NPH) is a treatable type of dementia with clinical improvement rates 70-90% by using modern diagnostic and therapeutic methods.

- NPH is characterized by combination of clinical and radiological features.

- Primary (idiopathic) NPH is distinguished from secondary NPH.

- Typical clinical features (Hakim triad) are gait impairment, dementia and urinary incontinence.
  - Gait impairment: short-stepped, broad based, slow, glue-footed walk with externally rotated posture of feet and particular difficulty turning on the body’s long axis.
  - Dementia: psychomotor slowing, impaired attention and concentration, short-term memory impairment esp. of delayed recall, apathy, reduced drive.
  - Urinary incontinence: detrusor hyperactivity with disturbed inhibitory control.

*Kiefer & Unterberg 2012*
Summary

- Cerebral imaging: disproportionate widening of the ventricles in comparison to the cerebral sulci (inner vs. outer CSF spaces) and surrounding the outer surface of the brain (‘tight convexity’) narrow subarachnoid space

- Spinal tap test: lumbar puncture with removal of 30-70 mL of CSF. The test should be considered positive when walking time or walking distance improve at least 20-30% and/or the cognitive performance improve at least 10%.

- Standard treatment of NPH is the implantation of a ventriculoperitoneal (VP) shunt. Clinical improvement rates of the surgery in studies aprox. 70-90%.

*Kiefer & Unterberg 2012*
Therapy of dementia – Improvement of Quality of Life
ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΥΠΟΜΟΝΗ ΚΑΙ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ!
THANK YOU VERY MUCH FOR YOUR PATIENCE AND ATTENTION
Case report 1

Hospitalisation of a 77 year old woman in 2014:
F31.8: bipolar II affective disorder, currently depressive episode
F06.7: mild cognitive impairment

Admission because of a prolonged depressive episode with social isolation.

Case history:
-Bipolar affective disorder since 20 years old
-Since 2010 more frequent phase-switches, attention- and memory-problems, intermittently gait impairment and intermittently urinary incontinence.
-In 2011 Memory Clinic Tests with diagnosis of MCI and neurological exams incl. Spinal-tap-test excluded NPH.
-Family history: brother (81y) Alzheimer’s dementia in early stage.
Case report 1

Psychopathology:
No disorders of consciousness. Oriented to all dimensions. **Prominent deficits of attention, concentration as well as memory.** Formal thought lightly intricate. No Ego-disturbances. No hallucinations. 
**Depressed mood.** Emotional flexibility and drive reduced. Reduced **psychomotor activity.** Appetite normal. No anxiety. No suicidal thoughts, activities or plans.

Somatic and neurological examination:
Walking insecure, wide-based and small stepped. Tendency to fall backwards. Urinary incontinence.
Case report 1

neuropsychological report:

neuropsychological impairment according currently depressive episode
DD: MCI

MMSE: 24/30
Case report 1

cMRI:
Case report 1
 voxelbased volumetry of the cMRI:

Hippokampus

Koronare Schichten des Hippokampus

Weisse Linie: Rand der Hippokampus-Maske

Farbig markierte Bereiche:
Graue Substanz reduziert (alterskorrigiert):
p < 0.05

Ausschnitt [1] Normal 76 Jahre

Graue Substanz im Hippokampus Gesamtvolumen: 3.8 ± 0.3 ml

Case report 1
voxel based volumetry of the cMRI:
Case report 1

Lumbal puncture:

Albumin Liquor: 505 mg/l (110-350)
Albuminquotient: 12.6 (<9.7)
IgG: 41.7 mg/l (<34)

Reiber-schema: no intrathecal immunglobuline-synthesis

Amyloid, Beta-Proteine: 455pg/ml (576-1012)
Phosphotau-Proteine: 47pg/ml (< 61)
Tau-Proteine: 216pg/ml (<500)
Case report 1

Spinal-tap-test (removal of 50ml CSF):

- gait improvement 12%
- impressive improvement of subjective wellbeing, patient felt more awake 2 days long after CSF removal

→ admission to neurosurgery: VP shunt implantation
Case report 1

Medication:

Venlafaxine 75mg/d – drug level in blood 0.74 µmol/l (nausea/ vomiting with drug level of 112.5mg/d)

Lamotrigine 50mg/d
Case report 1 - outcome

1 month after VP-shunt-implantation:
- Progressive clinical improvement
- Gait: fluent, large stepped. No tendency to fall anymore. Urinary incontinence.
- MMSE 30/30.

1 year after VP-shunt-implantation:
- Further clinical improvement
- Gait: secure, quickly, large stepped, no broad based, no tendency to fall.
- MMSE 30/30.

Patient lives alone, independently, without restriction in ADL’s, at her home.
Case report 2

Hospitalisation of the 79 year old woman:
Admission to our special unit for dementia from a somatic hospital because of major deficits in performing activities of daily living, disorientation and intermittent hallucinations. Somatic, cardiologic as well as the red and white cell examination was normal.

Case history:
In the months before admission she became increasingly forgetful, often irritable and refusing. In addition she showed cognitive and physical decline as well as social isolation. Finally, she was obviously confused and physically deprived.
Case report

Psychopathology:
No disorders of consciousness. **Disoriented to all dimensions.** Prominent deficits of attention, concentration as well as memory. Formal thought disorders as retarded thinking. No Ego-disturbances. **Optical and acoustical hallucinations** have been observed. **Contentual thought disorders** as delusion of impoverishment. Depressed mood. Emotional flexibility and drive reduced. **Reduced psychomotor activity.** Appetite normal. **Sleep lightly impaired.** No anxiety. No suicidal activities or plans but sometimes wish of death.

Somatic and neurological examination:
**Walking extremely insecure, wide-based, slow, shuffling step and impaired capacity to rotate.** Urinary incontinence.
Case report - Diagnostics

Psychometric testing:
Mini Mental State Examination (MMSE): 14/30
Clock-Test: 0/5
DemTect: 6/18
Geriatric Depression Scale (GDS): 7

Laboratory diagnostics:
Normal.
Case report – Brain imaging
Case report - Course and treatment

Clinical triad: Gait disturbance, dementia, urinary incontinence.

Brain imaging: Resorption disturbance of cerebrospinal fluid.

Lumbal puncture: Drainage of 45ml cerebrospinal fluid.

Measuring of the walking distance:

Before drainage: 3’26“
4h after drainage: 2’24“
24h after drainage: 2’11“

Outcome:

The walking patterns (speed, distance, movement, confidence) improved significantly.
Case report - Outcome

NPH - vor LP MOV00914.3GP

NPH - 24h nach LP MOV00917.3GP
Case report – Therapy and outcome

Diagnosis: Normal Pressure Hydrocephalus

Further therapy:
Implantation of ventriculoperitoneal shunt, treatment and rehabilitation.

Outcome:
Within a few weeks after shunting the presentation further improved. She became continent, her walking normalized nearly completely, she no longer fell and her cognitive performance improved subjectively as well as objectively.
References


Levine DN. Intracranial pressure and ventricular expansion in hydrocephalus: have we been asking the wrong question? *J Neurol Sci* 2008;269:1-11.


ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΥΠΟΜΟΝΗ ΚΑΙ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ!
THANK YOU VERY MUCH FOR YOUR PATIENCE AND ATTENTION
Pathophysiology

In the pathophysiology of NPH there is agreement on a multifactorial nature:

1. Mechanical stretching of long fibers (Johanson, 2003)

2. Reduction of regional cerebral blood flow (with periventricular ischemia) (Momjian et al., 2004)

3. Stagnation of CSF with accumulation of toxic wastes (Silverberg, 2004)
NPH & Alzheimer

To determine the impact of cortical Alzheimer disease pathology on shunt responsiveness in individuals treated for idiopathic normal pressure hydrocephalus (iNPH), 37 patients clinically diagnosed with iNPH participated in a prospective study in which performance on neurologic, psychometric, and gait measures before and 4 months after shunting was correlated with amyloid β plaques, neuritic plaques, and neurofibrillary tangles observed in cortical biopsies obtained during shunt insertion. No complications resulted from biopsy acquisition. Moderate to severe pathology was associated with worse baseline cognitive performance and diminished postoperative improvement on NPH symptom severity scales, gait measures, and cognitive instruments compared to patients lacking pathology.

Lack of Shunt Response in Suspected Idiopathic Normal Pressure Hydrocephalus with Alzheimer Disease Pathology

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ANN NEUROL 2010;68:535–540
NPH & Alzheimer

![Images showing different types of plaques and pathology](image)

**TABLE 1: Prevalence and Severity of Cortical Pathology (N=37)**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Absent</th>
<th>Rare</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ plaques</td>
<td>12 (32.4%)</td>
<td>0 (0%)</td>
<td>6 (16.2%)</td>
<td>12 (32.4%)</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Neuritic plaques</td>
<td>14 (37.8%)</td>
<td>0 (0%)</td>
<td>9 (24.3%)</td>
<td>14 (37.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tau</td>
<td>27 (73.0%)</td>
<td>4 (10.8%)</td>
<td>6 (16.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Aβ = amyloid β.

*Hamilton et al., 2010*