

NEUROTRANSMITTER MEASURES IN THE CEREBROSPINAL FLUID OF PATIENTS WITH ALZHEIMER'S DISEASE: A REVIEW

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SUMMARY

Background: Alzheimer's disease (AD) is a severe neurodegenerative disorder characterized by progressive cognitive and functional decline, as well as by a variety of neuropsychiatric and psychological symptoms and behavioral dysfunctions. Various studies proposed the role of different neurotransmitter systems not only in AD-related cognitive, but also psychotic symptoms and behavioral and emotional deficits. Due to the close proximity, pathological neurochemical changes in brain occurring in AD are likely to be reflected in the cerebrospinal fluid (CSF). The purpose of this review is to provide a summary of the CSF neurotransmitter correlates of AD in order to get further insights into the potential role of altered neurotransmitters in the pathophysiology of AD and to offer novel AD biomarkers.

Methods: PubMed and MEDLINE data bases were searched for English-language articles by using "Alzheimer's disease", "CSF" and "neurotransmitter" as primary terms. No time or article type constraints were applied. Moreover, the lists of references were searched manually for additional articles.

Results: Changes in various correlates of cholinergic, monoaminergic and amino acid neurotransmitter systems, as well as neuropeptides, have been observed in CSF of AD patients. However, as the results of these studies have been controversial, the importance of CSF neurotransmitter parameters as potential biomarkers in AD remains quite unclear. The observed discrepancies could be bypassed by implementation of new sensitive methods, such as novel proteomics approaches that include protein separation techniques, mass spectroscopy and targeted multiplex panels of specific analytes.

Conclusion: Although no individual CSF neurotransmitter correlate was demonstrated as suitable biomarker of AD, a combined profile of several CSF neurochemical parameters might show enhanced sensitivity and specificity and thus contribute to earlier and more accurate diagnosis of AD, crucial for application of effective treatments.

Key words: Alzheimer's disease - biomarkers - CSF - neurotransmitters – review

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INTRODUCTION

Alzheimer's disease (AD) is a severe age-related neurodegenerative disorder characterized by a progressive cognitive and functional decline, as well as with a variety of neuropsychiatric and psychological symptoms and behavioral dysfunctions (Wuwongse et al. 2010). The major pathological features of AD are progressive loss of basal forebrain cholinergic neurons, as well as accumulation of extracellular senile plaques formed mainly of the amyloid- β peptide (A β), and intracellular neurofibrillary tangles (NFT), which contain hyperphosphorylated tau (P-tau) (Armstrong et al. 2013, Ubhi & Masliah 2013). It has been suggested that AD is a complex multifactorial disorder, with many proposed theories as to the cause of AD, including those based on aging, degeneration of anatomical pathways, environmental factors, genetic factors, mitochondrial dysfunction, vascular factors, immune system dysfunction, and infectious agents (Armstrong et al. 2013). However, despite extensive and long-lasting research, there is still no cure, no prevention, and only limited symptomatic treatment options, in part due to the current inability of early AD diagnosis.

Although AD primarily affects brain regions involved in learning and memory, such as the neocortex and

the hippocampus (Rodriguez et al. 2012), in addition to its primary effects on cognition, "noncognitive" neuropsychiatric symptoms are present in great majority of AD patients (Lee & Lyketsos 2003, Geda et al. 2013). The mood and behavioral disturbances in AD, including agitation, anxiety, depression, apathy, psychosis, as well as sleep or appetite impairments (Lyketsos et al. 2000, Geda et al. 2013), have various adverse consequences for patients, such as greater impairment in the activities of daily living (Lyketsos et al. 1997), more rapid cognitive decline (Stern et al. 1997), worse quality of life (Gonzales-Salvador et al. 2000), earlier institutionalization (Steele et al. 1990), as well as greater caregiver depression (Gonzales-Salvador et al. 1999). The prevalence of these behavioral and emotional symptoms has been estimated to be 3 to 4 times higher in AD patients than in aged persons without dementia (Lyketsos & Olin 2002).

Hence, is not surprising that although current AD pharmacotherapy focuses mainly on impairment of cholinergic and glutamatergic systems (Chu et al. 2012), in addition to acetylcholine esterase inhibitors (donepezil, rivastigmine, galantamine) and cognitive enhancers (memantine), a variety of drugs is used in order to relieve behavioral and psychological symptoms of dementia (BPSD) (Rojas-Fernandez et al. 2001, Amano et

al. 2009, Gauthier et al. 2010). These other drugs used in the therapy of AD patients with BPSD include antipsychotics, antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors), anti-insomnia drugs, anxiolytic as well as anticonvulsant drugs (Aupperle 2006, Henry et al. 2011, Yeh & Ouyang 2012).

A vast number of experimental studies suggested progressive loss of neuronal synapses and consequent disturbance of different neurotransmitter pathways in AD (Reinikainen et al. 1990, Francis et al. 2010, Xu et al. 2012). Various studies proposed the role of different neurotransmitters (including their transporters and receptors), such as serotonin, noradrenaline, acetylcholine, dopamine and N-methyl-d-aspartate, as crucial neuroregulators, whose pathological alterations contribute to cognitive impairments and/or deterioration in AD (Kevin et al. 2011, Xu et al. 2012). However, these neurotransmitter systems are involved not only in AD-related cognitive, but also behavioral deficits (Lanari et al. 2006, Rodriguez et al. 2012, Vermeiren et al. 2014a,b). Namely, research suggests that altered activities and imbalance of cholinergic, dopaminergic, serotonergic, (nor)adrenergic, as well as amino acid neurotransmitter systems are particularly involved in the etiopathogenesis of BPSD (Herrmann et al. 2004, Garcia-Alloza et al. 2005, 2006, Lanctôt et al. 2001, 2007, Chen et al. 2011, Pinto et al. 2011, Vermeiren et al. 2013).

Due to close proximity of brain parenchyma and cerebrospinal fluid (CSF), pathological changes in brain occurring in AD are likely to be reflected in the CSF (Raedler & Wiedemann 2006). Hence, as in the case of other CSF biomarkers (tau, P-tau and A β 42), CSF levels of different neurotransmitters might be also correlated with neurochemical alternations in AD brain (Beal & Growdon 1986), cognitive decline (Kawakatsu et al. 1990, Kester et al. 2009), as well as with noncognitive AD symptoms (Roe et al. 2013, Vermeiren et al. 2013). The purpose of this review is to provide a summary of previous findings regarding CSF neurotransmitter correlates of AD in order to get further insights into their potential role in improvement of AD current biomarkers.

METHODS

To perform a comprehensive review of the literature focusing on the studies of CSF neurotransmitters in AD, an electronic search of English-language articles was conducted using PubMed and MEDLINE. The primary search with terms “Alzheimer's disease”, “CSF” and “neurotransmitter” yielded initially 262 references, 254 of them in English. No time or article type constraints were applied. Relevant scientific literature including original research articles, reviews, and other articles of interest were systematically reviewed, and the most important data was extracted. Moreover, the lists of references were searched manually for additional articles. Finally, out of 133 citations, 97 references specifically

regarding CSF neurotransmitters in AD were selected and included in this review providing a summary of these findings as well as their critical appraisal.

ACETYLCHOLINE

Specific degeneration of cholinergic neurons, down-regulation of choline acetyltransferase, the enzyme responsible for the synthesis of acetylcholine (ACh), as well as reduced choline uptake and ACh release, resulting in severe deficits of cholinergic neurotransmitter system function, have been observed in AD patients (Francis et al. 1999, Schliebs & Arendt 2011). Cholinergic replacement, using acetylcholine esterase inhibitors, which improves cognitive functions, is one of the few available and effective strategies for the treatment of AD. Ionotropic nicotinic (nAChR) and metabotropic muscarinic (mAChR) acetylcholine receptors, which both mediate acetylcholine-induced neurotransmission, have been also affected in AD (Jiang et al. 2014, Lombardo & Moskos 2014). It has been suggested that observed reduction in the number of AChR occurs in the early stages of the pathological process and is closely associated with primary histopathological changes in AD, such as amyloid plaques and neurofibrillary tangles (Kihara & Shimohama 2004).

These findings suggest that peripheral markers of central cholinergic activity may be also useful in the diagnosis of this disease. ACh concentrations in CSF of AD patients were found to be significantly lower than in control subjects, while ACh deficit correlated positively with cognitive impairment (Davis et al. 1985, Tohgi et al. 1994, Jia et al. 2004). Despite of ACh reductions observed in CSF of AD patients, some authors argued whether determination of ACh levels in CSF is suitable for diagnostic purposes of AD due to methodological limitations (Frolich et al. 1998). Increased concentrations of choline in CSF of AD patients have been also demonstrated, suggesting a disturbance in utilization of choline for ACh synthesis (Ikeda et al. 1990). However, some studies observed no differences in CSF choline levels between AD patients and normal controls (Tohgi et al. 1994, Jia et al. 2004).

Reduced CSF activity of acetylcholinesterase (AChE), nonspecific cholinesterase (nsChE) or butyrylcholinesterase (BuChE) has been reported in some (Appleyard et al. 1987, Atack et al. 1988, Kaye et al. 1988, Sirvio et al. 1989, Kawakatsu et al. 1990, Appleyard & McDonald 1992) but not in all AD studies (Marquis et al. 1985, Zubenko et al. 1986, Elble et al. 1987, Huff et al. 1989, Marksteiner et al. 2008). It has been demonstrated that AChE levels in CSF of AD patients closely mirror the in vivo brain AChE levels (Darreh-Shori et al. 2008), and that low AChE activities in CSF are associated with degrees of dementia as well as the Alzheimer-related symptoms of dyspraxia and dysphasia (Wester et al. 1988). Moreover, some authors reported that AChE species differ in their responses to disease and their interactions with A β and P-tau

(García-Ayllón et al. 2011). Studies addressing AChE - amyloid interrelationships indicated that AChE may participate in the pathological feedback loop between presenilin-1 (PS1) and A β (Silveyra et al. 2012), by increasing PS1 levels and inhibiting the γ -secretase activity (Campanari et al. 2014).

It has been hypothesized that CSF butyrylcholinesterase levels vary inversely with butyrylcholinesterase in cortical amyloid plaques and that low butyrylcholinesterase levels in AD patient's CSF could possibly predict extensive incorporation in neuritic plaques, increased neurotoxicity and greater central neurodegeneration (Darreh-Shori et al. 2006). The studies investigating the interrelationships between apolipoprotein E (ApoE) and butyrylcholinesterase levels, and pathological markers of AD in vivo, suggested that abnormally high levels of ApoE might be involved in the early cholinergic deficit in the AD brain, and that through modulation of cholinesterases activities may disturb the acetylcholine-dependent activity of neurons and glial cells (Darreh-Shori et al. 2011).

Decreased ratio of CSF acetylcholinesterase to butyrylcholinesterase activity (Arendt et al. 1984), as well as elevated ratio of acetylcholinesterase to nonspecific cholinesterase activities in CSF was observed in patients with AD (Appleyard et al. 1987). Some studies have also shown altered acetylcholinesterase and butyrylcholinesterase glycosylation in CSF, very specific for AD (Saez-Valero et al. 1997, 2000, Saez-Valero & Small 2001). However, subsequent results suggested that observed increased CSF levels of acetylcholinesterase and butyrylcholinesterase glycosylated forms are not likely to represent early markers of AD, although they may be useful as markers of disease progression (Saez-Valero et al. 2003).

MONOAMINE NEUROTRANSMITTERS

It has been suggested that CSF cholinergic deficits in AD are more often associated with cognitive decline than the deficits of other monoamines (Kawakatsu et al. 1990). However, the first detailed studies on CSF chemistry in relation to AD were reports from late 1960s and early 1970s about reduced CSF monoamine metabolite concentrations, suggesting a breakdown of these neurotransmitter systems in the deteriorating brain (Zetterberg & Blennow 2013). The concentrations of monoamine metabolites homovanilic acid (HVA), dihydroxyphenylacetic acid (DOPAC), and 5-hydroxyindolacetic acid (5-HIAA), as well as monoamine synthesis cofactor bipterin were found to be significantly decreased in AD (Soininen et al. 1981, Bareggi et al. 1982, Volicer et al. 1985b, Kay et al. 1986, Zubenko et al. 1986, Pinessi et al. 1987, Kaye et al. 1988a,b, Brane et al. 1989, Kawakatsu et al. 1990, Martignoni et al. 1991, Blennow et al. 1992, Parnetti et al. 1992, Sjogren et al. 1998). AD patients with severe forms of mental deterioration and senile dementia demonstrated most prominent decrease in the CSF levels of HVA and 5-

HIAA, which may reflect a decreased turnover of dopamine and serotonin (Soininen et al. 1981, Bareggi et al. 1982).

However, unaffected (Bareggi et al. 1982, Zimmer et al. 1984, Nybäck et al. 1991, Molchan et al. 1991, Parnetti et al. 1992, Toghi et al. 1992, Sheline et al. 1998, Stuerenburg et al. 2004) or elevated (Volicer et al. 1985b, Zubenko et al. 1986, van der Cammen et al. 2006) levels of HVA and 5-HIAA were also reported in AD. Although some authors found no differences in CSF levels of HVA and 5-HIAA between mild cognitive impairment, depression and AD, they observed elevated HVA levels in AD with depression in comparison to AD without depression, as well as positive correlation of 5-HIAA with A β 42 and HVA levels in CSF of AD patients (Stuerenburg et al. 2004). In addition to observed changes in the CSF levels of monoamine metabolites, findings of reduced CSF concentrations of neurotransmitters dopamine (Pinessi et al. 1987, Toghi et al. 1992) and serotonin (5-HT), as well as serotonin precursor 5-hydroxytryptophan (5-HTP) (Volicer et al. 1985a) suggested systemic damage of monoaminergic neurons in AD. Moreover, some authors reported abnormal, partially oxidized forms of 5-HT and 5-HTP in CSF of AD patients (Volicer et al. 1985a).

Although lower norepinephrine (NE) levels and degeneration of noradrenergic neurons have been observed in the brain of AD patients, the aging-associated high CSF concentrations of NE are retained in the earlier stages of AD and are significantly higher in the patients with advanced stage of the disease (Elrod et al. 1997, Raskind et al. 1999). However, some studies revealed no changes (Toghi et al. 1992), as well as significant reduction (Martignoni et al. 1991) in CSF NE levels in AD patients. Observed increased CSF levels of NE precursor dihydroxyphenylacetic acid (DOPA) in older and AD patients than in young subjects following alpha-2 adrenoceptor blockade with yohimbine suggested particularly prominent compensatory activation of remaining CNS noradrenergic neurons (Raskind et al. 1999). CSF levels of NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) were shown to be unchanged (Volicer et al. 1985b, Nybäck et al. 1991, Molchan et al. 1991, Parnetti et al. 1992, Blennow et al. 1992), lower (Sjogren et al. 1998) or higher (Brane et al. 1989, Toghi et al. 1992) in patients with AD than in control subjects, and inversely correlated with cognitive function (Gibson et al. 1985, Sheline et al. 1998). Higher CSF levels of epinephrine (EPI) were also found in AD and increased further with dementia severity in AD patients (Peskind et al. 1998).

AMINO-ACID NEUROTRANSMITTERS

Glutamate, as major fast excitatory neurotransmitter in the brain, is involved in almost all CNS functions; however it plays especially important role in neuronal plasticity underlying learning and memory. The variety of evidence suggests that glutamatergic system and particularly

Table 1. Changes in the main components of different neurotransmitter systems observed in the CSF of AD patients

Neurotransmitter System component	Change in AD	Reference
Acetylcholine	decrease	Davis et al. 1985, Tohogi et al. 1994, Jia et al. 2004
Choline	increase	Ikeda et al. 1990
	no changes	Tohogi et al. 1994, Jia et al. 2004
Acetylcholinesterase	decrease	Appleyard et al. 1987, Atack et al. 1988, Kaye et al. 1988, Sirvio et al. 1989, Kawakatsu et al. 1990, Appleyard & McDonald 1992, Darreh-Shori et al. 2006, 2008, Wester et al. 1988
Nonspecific cholinesterase		
Butyrylcholinesterase	no changes	Marquis et al. 1985, Zubenko et al. 1986, Elble et al. 1987, Huff et al. 1989, Marksteiner et al. 2008
Homovanilic acid (HVA)	decrease	Soininen et al. 1981, Bareggi et al. 1982, Volicer et al. 1985b, Kay et al. 1986, Zubenko et al. 1986, Pinessi et al. 1987, Kaye et al. 1988a,b, Brane et al. 1989, Kawakatsu et al. 1990, Martignoni et al. 1991, Blennow et al. 1992, Parnetti et al. 1992, Sjogren et al. 1998
Dihydroxyphenylacetic acid (DOPAC)		
5-hydroxyindolacetic acid (5-HIAA)	no change	Bareggi et al. 1982, Zimmer et al. 1984, Nybäck et al. 1991, Molchan et al. 1991, Parnetti et al. 1992, Toghi et al. 1992, Sheline et al. 1998, Stuerenburg et al. 2004
Biopterin	increase	Volicer et al. 1985b, Zubenko et al. 1986, van der Cammen et al. 2006
Dopamine	decrease	Pinessi et al. 1987, Toghi et al. 1992
Serotonin (5-HT)	decrease	Volicer et al. 1985a
5-hydroxytryptophan (5-HTP)		
Norepinephrine (NE)	increase	Elrod et al. 1997, Raskind et al. 1999
	no change	Toghi et al. 1992
	decrease	Martignoni et al. 1991
Dihydroxyphenylacetic acid (DOPA)	increase	Raskind et al. 1999
3-methoxy-4-hydroxy-phenylglycol (MHPG)	increase	Brane et al. 1989, Toghi et al. 1992
	decrease	Sjogren et al. 1998
	no change	Volicer et al. 1985b, Nybäck et al. 1991, Molchan et al. 1991, Parnetti et al. 1992, Blennow et al. 1992
Epinephrine (EPI)	increase	Peskind et al. 1998
Gamma-aminobutyric acid (GABA)	increase	Samakashvili et al. 2011
	decrease	Enna et al. 1977, Kuroda 1983, Zimmer et al. 1984
	no change	Bareggi et al. 1982
Glutamine	increase	D'Aniello et al. 2005
	decrease	Smith et al. 1985, Kuiper et al. 1994, 2000
	decrease	Samakashvili et al. 2011
Glutamate	increase	Jimenez-Jimenez et al. 1998, Kaiser et al. 2010
	decrease	Raskind et al. 1986, Kuiper et al. 1994, 2000
	no change	Smith et al. 1985, Ferrarese et al. 2001
Nitrate	decrease	Kuiper et al. 1994, 2000
	no change	Navarro et al. 1996
Glycine	increase	Jimenez-Jimenez et al. 1998
Asparagine	decrease	Jimenez-Jimenez et al. 1998, Samakashvili et al. 2011
Arginine	decrease	Raskind et al. 1986
Lysine		
L-aspartate	decrease	D'Aniello et al. 2005
Somatostatin	decrease	Raskind et al. 1986, Gomez et al. 1986, Sunderland et al. 1987, Hartikainen et al. 1992, Edvinsson et al. 1993, Molchan et al. 1992, 1993, Yasuda et al. 1995, Strittmatter et al. 1997, Nilsson et al. 2001, Cramer et al. 1985, Strittmatter et al. 1997, Minthon et al. 1997
Somatostatin-like immunoreactivity (sli)		
Prepro-somatostatin (prepro-ss)/ss-28		
Y-immunoreactivity (NPY-ir)	no changes	Heilig et al. 1995
	decrease	Martignoni et al. 1992, Edvinsson et al. 1993, Nilsson et al. 2001; Yasuda et al. 1995 Cramer et al. 1985, Strittmatter et al. 1997, Minthon et al. 1997

Table 1. Continuous

Neurotransmitter System component	Change in AD	Reference
Histidine methionine immunoreactivity	no changes	Yasuda et al. 1995
Histidine valine		
Histidine methionine 27	increase	Marksteiner et al. 2008
Vasoactive intestinal peptide (vip)		
Mature nerve growth factor (NGF)-like immunoreactivity	increase	Rosler et al. 2001
Substance P-like-immunoreactivity	decrease	Cramer et al. 1985
	decrease	May et al. 1987, Suemaru et al. 1991, 1993, Heilig et al. 1995
Adrenocorticotrophic hormone (ACTH)	increase	Heilig et al. 1995
Delta-sleep-inducing peptide	decrease	Ernst et al. 1987, Edvinsson et al. 1993
	increase	Banki et al. 1992
Corticotrophin-releasing hormone (CRH)	decrease	May et al. 1987, Suemaru et al. 1991, 1993, Heilig et al. 1995
	no changes	Pomara et al. 1989, Edvinsson et al. 1993
	increase	Nilsson et al. 2001
Galanin	decrease	Mazurek et al. 1986, Raskind et al. 1986
Arginine vasopressin	no change	Jolkkonen et al. 1989
	no change	Raskind et al. 1986
Oxytocin	no change	Raskind et al. 1986
Beta-endorphine	decrease	May et al. 1987, Suemaru et al. 1991, 1993, Heilig et al. 1995
	no change	Raskind et al. 1986

ionotropic glutamate N-methyl-D-aspartate (NMDA) receptors play a significant role in synaptic dysfunction and neuronal death, as well as in cognitive deficits in AD (Wenk et al. 2006). Strong support for relevance of interactions between A β , glutamate and NMDA receptors in AD is provided by the NMDA receptor antagonist memantine, used clinically in the treatment of this disease (Dansyz & Parsons 2012). In CSF of AD patients, observed lower concentration of glutamate correlated with psychological measures (Smith et al. 1985), and was related to the degree of dementia (Ferrarese et al. 2001). However, glutamate was also found to be significantly elevated in the CSF of patients with AD (Jimenez-Jimenez et al. 1998, Kaiser et al. 2010). These findings also suggest that glutamate metabolism is altered in AD and that glutamatergic neurons are not spared in this disorder.

Reduced levels of major inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in CSF were also observed in patients with AD (Enna et al. 1977, Kuroda 1983, Zimmer et al. 1984). Some authors demonstrated that GABA levels decreased with age, however when compared with the age-matched controls, patients with AD showed no changes in GABA concentrations (Bareggi et al. 1982). Although glycine and glutamine in the CSF of AD samples were found to be lower than these measures in control samples (Smith et al. 1985), some authors observed higher CSF glycine levels, as well as lower asparagine levels in AD patients (Jimenez-Jimenez et al. 1998). By using enantioselective proce-

dures, Samakashvili and colleagues investigated D- and L-amino acid contents in CSF samples related to different AD stages and observed lower amounts of L-arginine, L-lysine, L-glutamate and L-asparagine and higher levels of GABA in AD subjects (Samakashvili et al. 2011). Much higher levels of L-glutamine and lower concentrations of L-aspartate, also observed in CSF of AD patients, are suggested to be the consequence of the higher activity of glutamic oxaloacetate transaminase (GOT) that occurs in Alzheimer brain (D'Aniello et al. 2005). As biosynthesis of nitric oxide (NO) is dependent on the L-glutamate, which stimulates nitric oxide synthesis via the NMDA receptor, the findings of decreased levels of L-glutamate and nitrate (nitric oxide degradation product) in CSF of AD patients, suggested that AD is associated with a decrease in nitric oxide CNS production (Kuiper et al. 1994, 2000). In contrast, some results demonstrating no changes in CSF nitrate levels suggested that they are apparently unrelated with the risk of AD (Navarro et al. 1996).

NEUROPEPTIDES

Studies of CSF neuropeptides suggested that various neuropeptide systems are differentially affected by neurodegeneration. Namely, decreased somatostatin-like immunoreactivity (SLI) (Raskind et al. 1986, Gomez et al. 1986, Sunderland et al. 1987, Hartikainen et al. 1992, Edvinsson et al. 1993, Molchan et al. 1992, 1993, Yasuda et al. 1995, Strittmatter et al. 1997,

Nilsson et al. 2001), as well as reduction in neuropeptide Y-immunoreactivity (NPY-ir) (Martignoni et al. 1992, Edvinsson et al. 1993, Nilsson et al. 2001), has been observed in CSF of patients with AD. The correlations of somatostatin and neuropeptide Y to the clinical signs of AD disorientation and dyspraxia were found and somatostatin showed a significant negative correlation with severity of dementia in AD (Cramer et al. 1985, Strittmatter et al. 1997, Minthon et al. 1997). Measurement of molecular forms of somatostatin in CSF revealed significant loss of somatostatin-14 (SST-14) in AD which was correlated with dementia scores (Strittmatter et al. 1997). These qualitative and quantitative changes in the molecular pattern of somatostatin-like immunoreactivity in AD indicated dysregulated synthesis and/or processing of somatostatin relating to the severity of dementia (Strittmatter et al. 1997). The concentrations of SS-28, peptide derived from prepro-somatostatin (prepro-SS), were found to be significantly reduced in AD, while somatostatin-14 levels in AD patients did not differ from those of controls (Yasuda et al. 1995). These results suggested that an altered processing of the prepro-peptides of somatostatin may occur in AD and that these alterations might have a significant role in the pathogenesis of this disease.

Reduced levels of total peptide histidine methionine immunoreactivity and peptide histidine valine, as well as unaltered levels of peptide histidine methionine 27 and vasoactive intestinal peptide (VIP) were observed in AD (Yasuda et al. 1995). On the other hand, mature nerve growth factor (NGF)-like immunoreactivity, but not anti-NGF auto-antibody levels, was found enhanced in AD patients (Marksteiner et al. 2008). Patients with late onset AD (>65 years) showed significantly higher levels of substance P-like-immunoreactivity than patients with early onset (<65 years) and controls (Rosler et al. 2001). Substance P-like-immunoreactivity correlated with somatostatin-like immunoreactivity in AD patients, but was decreased significantly only in late onset AD patients (Cramer et al. 1985). Moreover, CSF concentrations of corticotrophin-releasing hormone (CRH), beta-endorphine, somatostatin (SRIF, somatotropin release-inhibiting factor) and adrenocorticotrophic hormone (ACTH) were markedly lower, and delta-sleep-inducing peptide was increased in AD patients, while beta-endorphine levels correlated negatively with degree of dementia (May et al. 1987, Suemaru et al. 1991, 1993, Heilig et al. 1995). However, opposite results such as strong reduction in the levels of delta-sleep-inducing peptide (Ernst et al. 1987, Edvinsson et al. 1993), no changes in neuropeptide Y levels (Heilig et al. 1995), as well as unchanged (Pomara et al. 1989, Edvinsson et al. 1993) or even elevated (Banki et al. 1992) CRH levels were also observed in CSF of AD patients. It has been shown that galanin levels increased with the duration of illness in AD patients (Nilsson et al. 2001). The CSF arginine vasopressin concentrations were found unchanged (Jolkkonen et al. 1989) or decreased (Mazurek et al. 1986, Raskind et al. 1986) in patients

with AD, while oxytocin and beta-endorphin levels did not differ between patients with AD, normal elderly subjects and normal young subjects (Raskind et al. 1986).

CONCLUSION

A variety of data suggested that coupling of clinical/neurological parameters to different CSF profiles could improve early, accurate diagnosis of AD, which is a key to maximize disease-modifying treatment benefits (Blennow et al. 2010). While CSF tau, P-tau and A β have become part of the diagnostic process in clinical routine (Andreasen et al. 2003, Blennow et al. 2010), the importance of other CSF neurochemical parameters as potential biomarkers in AD remains quite unclear. Namely, no individual CSF neurotransmitter correlate was found as suitable biomarker of AD. However, as the results of previous studies suggest that AD pathophysiology involves early changes in functionally connected networks across many brain regions, there is an urgent need for broader biomarker investigations that should lead to better understanding of early disease mechanisms and help diagnose AD in the preclinical and early clinical stages (Shaw et al. 2007, Trushina et al. 2013).

The above reviewed variability regarding CSF neurotransmitter research is probably due to differences in sampling and used methodology. Therefore, in order to discover sensitive and specific biomarkers for AD, standardization of methods (CSF extraction, CSF gradient effects, storage, etc.) is essential for reducing inconsistency and increasing reliability, while consensus protocols of analysis are of critical importance (Cedazo-Minguez & Winblad 2010). Moreover, discrepancies between findings could be bypassed by implementation of new sensitive methods, such as novel proteomics approaches that include protein separation techniques, mass spectroscopy and targeted multiplex panels of specific analytes (Choi et al. 2010, Blennow et al. 2010, Czech et al. 2012, Trushina et al. 2013, Kovac et al. 2014).

The new approaches have already determined a number of candidate combinations, many of them in different neurotransmitter pathways, that could improve on the "core" protein biomarkers tau, P-tau and A β 42. Although none has been yet validated enough to be included in clinical practice, the combined profiles of several neurochemical markers from CSF might demonstrate enhanced sensitivity and specificity, and thus contribute to earlier and more accurate diagnosis, crucial for successful therapy of both AD cognitive and behavioral symptoms.

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References

1. Amano N, Inuzuka S, Ogihara T: Behavioral and psychological symptoms of dementia and medical treatment. *Psychogeriatrics* 2009; 9:45-9.
2. Andreasen N, Sjögren M, Blennow K: CSF markers for Alzheimer's disease: total tau, phospho-tau and Abeta42. *World J Biol Psychiatry* 2003; 4:147-55.
3. Appleyard ME & McDonald B: Acetylcholinesterase and butyrylcholinesterase activities in cerebrospinal fluid from different levels of the neuraxis of patients with dementia of the Alzheimer type. *J NeurolNeurosurg Psychiatry* 1992; 55:1074-8.
4. Appleyard ME, Smith AD, Beran P, Wilcock GK, Esiri MM, Neary D, et al.: Cholinesterase activities in cerebrospinal fluid of patients with senile dementia of Alzheimer type. *Brain* 1987; 110:1309-22.
5. Arendt T, Bigl V, Ealther F, Sonntag M: Decreased ratio of CSF acetylcholinesterase to butyrylcholinesterase activity in Alzheimer's disease. *Lancet* 1984; 21:173.
6. Armstrong RA: What causes Alzheimer's disease? *Folia Neuropathol* 2013; 51:169-88.
7. Atack JR, May C, Kaye JA, Kay AD, Rapoport SI: Cerebrospinal fluid cholinesterases in aging and in dementia of the Alzheimer type. *Ann Neurol* 1988; 23:161-7.
8. Aupperle P: Management of aggression, agitation, and psychosis in dementia: focus on atypical antipsychotics. *Am J Alzheimers Dis Other Demen* 2006; 21:101-8.
9. Banki CM, Karmacs L, Bissette G, Nemeroff CB: Cerebrospinal fluid neuropeptides in mood disorder and dementia. *J Affect Disord* 1992; 25:39-45.
10. Bareggi SR, Franceschi M, Bonini L, Zecca L, Smirne S: Decreased CSF concentrations of homovanillic acid and gamma-aminobutyric acid in Alzheimer's disease. Age- or disease-related modifications? *Arch Neurol* 1982; 39:709-12.
11. Beal MF & Gordon JH: CSF neurotransmitter markers in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 1986; 10:259-70.
12. Blennow K, Hampel H, Weiner M, Zetterberg H: Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nat Rev Neurol* 2010; 6:131-44.
13. Blennow K, Wallin A, Gottfries CG, Lekman A, Karlsson I, Skoog I, et al.: Significance of decreased lumbar CSF levels of HVA and 5-HIAA in Alzheimer's disease. *Neurobiol Aging* 1992; 13:107-13.
14. Brane G, Gottfries CG, Blennow K, Karlson I, Lekman A, Parnetti L, et al.: Monoamine metabolites in cerebrospinal fluid and behavioral ratings in patients with early and late onset of Alzheimer dementia. *Alzheimer Dis Assoc Disord* 1989; 3:148-56.
15. Campanari ML, García-Ayllón MS, Belbin O, Galcerán J, Lleó A, Sáez-Valero J: Acetylcholinesterase modulates presenilin-1 levels and γ -secretase activity. *J Alzheimers Dis* 2014; 41:911-24.
16. Cedazo-Minguez A & Winblad B: Biomarkers for Alzheimer's disease and other forms of dementia: Clinical needs, limitations and future aspects. *Exp Gerontol* 2010; 45:5-14.
17. Chen KH, Reese EA, Kim HW, Rapoport SI, Rao JS: Disturbed neurotransmitter transporter expression in Alzheimer's disease brain. *J Alzheimers Dis* 2011; 26:755-66.
18. Choi YS, Choe LH, Lee KH: Recent cerebrospinal fluid biomarker studies of Alzheimer's disease. *Expert Rev Proteomics* 2010; 7:919-29.
19. Chu LW: Alzheimer's disease: early diagnosis and treatment. *Hong Kong Med J* 2012; 18:228-37.
20. Cramer H, Schaudt D, Rissler K, Strubel D, Warter JM, Kuntzmann F: Somatostatin-like immunoreactivity and substance-P-like immunoreactivity in the CSF of patients with senile dementia of Alzheimer type, multi-infarct syndrome and communicating hydrocephalus. *J Neurol* 1985; 232: 346-51.
21. Czech C, Berndt P, Busch K, Schmitz O, Wiemer J, Most V, et al.: Metabolite Profiling of Alzheimer's Disease Cerebrospinal Fluid. *PLoS One* 2012; 7:e31501.
22. D'Aniello A, Fisher G, Migliaccio N, Cammisà G, D'Aniello E, Spinelli P: Amino acids and transaminases activity in ventricular CSF and in brain of normal and Alzheimer patients. *Neurosci Lett* 2005; 388:49-53.
23. Danysz W, Parsons CG: Alzheimer's disease, β -amyloid, glutamate, NMDA receptors and memantine--searching for the connections. *Br J Pharmacol* 2012; 167:324-52.
24. Darreh-Shori T, Brimijoin S, Kadir A, Almkvist O, Nordberg A: Differential CSF butyrylcholinesterase levels in Alzheimer's disease patients with the ApoE epsilon4 allele, in relation to cognitive function and cerebral glucose metabolism. *Neurobiol Dis* 2006; 24:326-33.
25. Darreh-Shori T, Forsberg A, Modiri N, Andreasen N, Blennow K, Kamil C, et al.: Differential levels of apolipoprotein E and butyrylcholinesterase show strong association with pathological signs of Alzheimer's disease in the brain in vivo. *Neurobiol Aging* 2011; 32:2320.e15-32.
26. Darreh-Shori T, Kadir A, Almkvist O, Grut M, Wall A, Blomquist G, et al.: Inhibition of acetylcholinesterase in CSF versus brain assessed by 11C-PMP PET in AD patients treated with galantamine. *Neurobiol Aging* 2008; 29:168-84.
27. Davis BM, Mohs RC, Greenwald BS, Mathé AA, Johns CA, Horvath TB, et al.: Clinical studies of the cholinergic deficit in Alzheimer's disease. I. Neurochemical and neuroendocrine studies. *J Am Geriatr Soc* 1985; 33:741-8.
28. Edvinsson L, Minthon L, Ekman R, Gustafson L: Neuropeptides in cerebrospinal fluid of patients with Alzheimer's disease and dementia with frontotemporal lobe degeneration. *Dementia* 1993; 4:167-171.
29. Elble R, Giacobini E, Scarsella GF: Cholinesterases in cerebrospinal fluid. A longitudinal study in Alzheimer disease. *Arch Neurol* 1987; 44:403-7.
30. Elrod R, Peskind ER, DiGiacomo L, Brodtkin KI, Veith RC, Raskind MA: Effects of Alzheimer's disease severity on cerebrospinal fluid norepinephrine concentration. *Am J Psychiatry* 1997; 154:25-30.
31. Enna SJ, Stern LZ, Wastek GJ, Yamamura HI: Cerebrospinal fluid gamma-aminobutyric acid variations in neurological disorders. *Arch Neurol* 1977; 34:683-5.
32. Ernst A, Cramer H, Strubel D, Kuntzmann F, Schoenberger GA: Comparison of DSIP- (delta sleep-inducing peptide) and P-DSIP-like (phosphorylated) immunoreactivity in cerebrospinal fluid of patients with senile dementia of Alzheimer type, multi-infarct syndrome, communicating hydrocephalus and Parkinson's disease. *J Neurol* 1987; 235:16-21.
33. Ferrarese C, Aliprandi A, Tremolizzo L, Stanzani L, De Micheli A, Dolara A, et al.: Increased glutamate in CSF and plasma of patients with HIV dementia. *Neurology* 2001; 57:671-5.

34. Francis PT, Palmer AM, Snape M, Wilcock GK: The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry* 1999; 66:137-147.
35. Francis PT, Ramirez MJ, Lai MK: Neurochemical basis for symptomatic treatment of Alzheimer's disease. *Neuropharmacology* 2010; 59:221-9.
36. Frolich L, Dirr A, Gitz MW, Gsell W, Reichmann H, Riederer P, et al.: Acetylcholine in human CSF: methodological considerations and levels in dementia of Alzheimer type. *J Neural Transm* 1998; 105:961-73.
37. Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M, Chen CP, Francis PT, Lasheras B, et al.: Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. *Neuropsychologia* 2005; 43:442-9.
38. Garcia-Ayllón MS, Small DH, Avila J, Sáez-Valero J: Revisiting the role of acetylcholinesterase in Alzheimer's Disease: cross-talk with P-tau and β -amyloid. *Front Mol Neurosci* 2011; 4:22.
39. Garcia-Alloza MG, Tsang SW, Gil-Bea FJ, Francis PT, Lai MK, Marcos B, et al.: Involvement of the GABAergic system in depressive symptoms of Alzheimer's disease. *Neurobiol Aging* 2006; 27:1110-1117.
40. Gauthier S, Cummings J, Ballard C, Brodaty H, Grossberg G, Robert P, et al.: Management of behavioral problems in Alzheimer's disease. *Int Psychogeriatr* 2010; 22:346-372.
41. Geda YE, Schneider LS, Gitlin LN, Miller DS, Smith GS, Bell J, et al.: Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *Alzheimers Dement* 2013; 9:602-8.
42. Gibson CJ, Logue M, Growdon JH: CSF monoamine metabolite levels in Alzheimer's and Parkinson's disease. *Arch Neurol* 1985; 42:489-92.
43. Gomez S, Davous P, Rondot P, Faivre-Bauman A, Valade D, Puymirat J: Somatostatin-like immunoreactivity and acetylcholinesterase activities in cerebrospinal fluid of patients with Alzheimer disease and senile dementia of the Alzheimer type. *Psychoneuroendocrinology* 1986; 11:69-73.
44. Gonzalez-Salvador T, Arango C, Lyketsos CG, Barba AC: The stress and psychological morbidity of the Alzheimer patient caregiver. *Int J Geriatr Psychiatry* 1999; 14:701-710.
45. Gonzalez-Salvador T, Lyketsos CG, Baker A, Hovanec L, Roques C, Brandt J, et al.: Quality of life of patients with dementia in long-term care. *Int J Geriatr Psychiatry* 2000; 15:181-189.
46. Hartikainen P, Reinikainen KJ, Soininen H, Sirvio J, Soikkeli R, Riekkinen PJ: Neurochemical markers in the cerebrospinal fluid of patients with Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis and normal controls. *J Neural Transm Park Dis Dement Sect* 1992; 4:53-68.
47. Heilig M, Sjorgen M, Blennow K, Ekman R, Wallin A: Cerebrospinal fluid neuropeptides in Alzheimer's disease and vascular dementia. *Biol Psychiatry* 1995; 38:210-6.
48. Henry G, Williamson D, Tampi RR: Efficacy and tolerability of antidepressants in the treatment of behavioral and psychological symptoms of dementia: a literature review of evidence. *Am J Alzheimers Dis Other Demen* 2011; 26:169-183.
49. Herrmann N, Lanctôt KL, Khan LR: The role of norepinephrine in the behavioral and psychological symptoms of dementia. *J Neuropsychiatry Clin Neurosci* 2004; 16:261-76.
50. Huff FJ, Reiter CT, Protetch J: Activities and kinetic properties of lumbar cerebrospinal fluid cholinesterases in relation to clinical diagnosis, severity, and progression of Alzheimer's disease. *Can J Neurol Sci* 1989; 16:406-10.
51. Ikeda Y, Okuyama S, Fujiki Y, Tomoda K, Ohshiro K, Itoh T, et al.: Changes of acetylcholine and choline concentrations in cerebrospinal fluids of normal subjects and patients with dementia of Alzheimer-type. *J Neural Transm Suppl* 1990; 30:25-3.
52. Jia JP, Jia JM, Zhou WD, Xu M, Chu CB, Yan X, et al.: Differential acetylcholine and choline concentrations in the cerebrospinal fluid of patients with Alzheimer's disease and vascular dementia. *Chin Med J (Engl)* 2004; 117:1161-4.
53. Jiang S, Li Y, Zhang C, Zhao Y, Bu G, Xu H, et al.: M1 muscarinic acetylcholine receptor in Alzheimer's disease. *Neurosci Bull* 2014; 30:295-307.
54. Jimenez-Jimenez FJ, Molina JA, Gomez P, Vargas C, de Bustos, Benito-Leon J, et al.: Neurotransmitter amino acids in cerebrospinal fluid of patients with Alzheimer's disease. *J Neural Transm* 1998; 105:269-77.
55. Jolkonen J, Helkala EL, Kutvonen R, Lehtinen M, Riekkinen PJ: Vasopressin levels in CSF of Alzheimer patients: correlations with monoamine metabolites and neuropsychological test performance. *Psychoneuroendocrinology* 1989; 14:89-95.
56. Kaiser E, Schoenknecht P, Kassner S, Hildebrandt W, Kinscherf R, Schroeder J: Cerebrospinal fluid concentrations of functionally important amino acids and metabolic compounds in patients with mild cognitive impairment and Alzheimer's disease. *Neurodegener Dis* 2010; 7:251-9.
57. Kawakatsu S, Morinobu S, Shinohara M, Totsuka S, Kobashi K: Acetylcholinesterase activities and monoamine metabolite levels in the cerebrospinal fluid of patients with Alzheimer's disease. *Biol Psychiatry* 1990; 28:387-400.
58. Kay AD, Milstien S, Kaufman S, Creasey H, Haxby JV, Cutler NR, et al.: Cerebrospinal fluid biopterin is decreased in Alzheimer's disease. *Arch Neurol* 1986; 43:996-9.
59. Kaye JA, May C, Atack JR, Daly E, Sweeney DL, Beal MF, et al.: Cerebrospinal fluid neurochemistry in the myoclonic subtype of Alzheimer's disease. *Ann Neurol* 1988a; 24:647-50.
60. Kaye JA, May C, Daly E, Atack JR, Sweeney DJ, Luxemburg JS, et al.: Cerebrospinal fluid monoamine markers are decreased in dementia of the Alzheimer type with extrapyramidal features. *Neurology* 1988b; 38:554-7.
61. Kester MI, van der Vlies AE, Blankenstein MA, Pijnenburg YA, van Elk EJ, Scheltens P, et al.: CSF biomarkers predict rate of cognitive decline in Alzheimer disease. *Neurology* 2009; 73:1353-8.
62. Kevin H, Chen KH, Reese EA, Kim HW, Rapoport SI, Rao JS: Disturbed Neurotransmitter Transporter Expression in Alzheimer Disease. *Brain J Alzheimers Dis* 2011; 26:755-766.
63. Kihara T & Shimohama S: Alzheimer's disease and acetylcholine receptors *Acta Neurobiol Exp* 2004; 64:99-105.
64. Kovac A, Somikova Z, Zilka N, Novak M: Liquid chromatography-tandem mass spectrometry method for determination of panel of neurotransmitters in cerebrospinal fluid from the rat model for tauopathy. *Talanta* 2014; 119:284-90.

65. Kuiper MA, Teerlink T, Visser JJ, Bergmans PL, Scheltens P, Wolters EC: L-glutamate, L-arginine and L-citrulline levels in cerebrospinal fluid of Parkinson's disease, multiple system atrophy, and Alzheimer's disease patients. *J Neural Transm* 2000; 107:183-9.
66. Kuiper MA, Visser JJ, Bergmans PL, Scheltens P, Wolters EC: Decreased cerebrospinal fluid nitrate levels in Parkinson's disease, Alzheimer's disease and multiple system atrophy patients. *J Neurol Sci* 1994; 121:46-9.
67. Kuroda H: Gamma-aminobutyric acid (GABA) in cerebrospinal fluid. *Acta Med Okayama* 1983; 37:167-77.
68. Lanari A, Ament F, Silvestrelli G, Tomassoni D, Parnetti L: Neurotransmitter deficits in behavioural and psychological symptoms of Alzheimer's disease. *Mech Ageing Dev* 2006; 127:158-165.
69. Lanctôt KL, Herrmann N, Mazzotta P: Role of serotonin in the behavioral and psychological symptoms of dementia. *J Neuropsychiatry Clin Neurosci* 2001; 13:5-21.
70. Lanctôt K, Herrmann N, Rothenburg L, Eryavec G: Behavioral correlates of GABAergic disruption in Alzheimer's disease. *Int Psychogeriatr* 2007; 19:151-158.
71. Lee HB & Lyketsos CG: Depression in Alzheimer's disease: heterogeneity and related issues. *Biol Psychiatry* 2003; 54:353-62.
72. Lyketsos CG & Olin J: Depression in Alzheimer's disease: overview and treatment. *Biol Psychiatry* 2002; 52:243-52.
73. Lombardo S & Maskos U: Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment. *Neuropharmacology* 2014; in press.
74. Lyketsos CG, Steele C, Baker L, Galik E, Kopunek S, Steinberg M, et al: Major and minor depression in Alzheimer's disease: Prevalence and impact. *J Neuropsychiatry Clin Neurosci* 1997; 9:556-561.
75. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC: Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* 2000; 157:708-14.
76. Marksteiner J, Pirchl M, Ullrich C, Oberbauer H, Blasko I, Lederer W, et al.: Analysis of cerebrospinal fluid of Alzheimer patients. *Biomarkers and toxic properties. Pharmacology* 2008; 82: 214-20.
77. Marquis JK, Volicer L, Mark KA, Direnfeld LK, Freedman M: Cholinesterase activity in plasma, erythrocytes, and cerebrospinal fluid of patients with dementia of the Alzheimer type. *Biol Psychiatry* 1985; 20: 605-10.
78. Martignoni E, Blandini F, Petraglia F, Pacchetti C, Bono G, Nappi G: Cerebrospinal fluid norepinephrine, 3-methoxyphenylglycol and neuropeptide Y levels in Parkinson's disease, multiple system atrophy and dementia of the Alzheimer type. *J Neural Transm Park Dis Dement Sect* 1992; 4:191-205.
79. Martignoni E, Bono G, Blandini F, Sinforiani E, Merlo P, Nappi G: Monoamines and related metabolite levels in the cerebrospinal fluid of patients with dementia of Alzheimer type. Influence of treatment with L-deprenyl. *J Neural Transm Park Dis Dement Sect* 1991; 3:15-25.
80. May C, Rapoport SI, Tomai TP, Chrousos GP, Gold PW: Cerebrospinal fluid concentrations of corticotropin-releasing hormone (CRH) and corticotropin (ACTH) are reduced in patients with Alzheimer's disease. *Neurology* 1987; 37:535-8.
81. Mazurek MF, Growdon JH, Beal MF, Martin JB: CSF vasopressin concentration is reduced in Alzheimer's disease. *Neurology* 1986; 36:1133-7.
82. Minthon L, Edvinsson L, Gustafson L: Somatostatin and neuropeptide Y in cerebrospinal fluid: correlations with severity of disease and clinical signs in Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord* 1997; 8:232-9.
83. Molchan SE, Hill JL, Martinez RA, Lawlor BA, Mellow AM, Rubinow DR, et al.: CSF somatostatin in Alzheimer's disease and major depression: relationship to hypothalamic-pituitary-adrenal axis and clinical measures. *Psychoneuroendocrinology* 1993; 18:509-19.
84. Molchan SE, Lawlor BA, Hill JL, Martinez RA, Davis CL, Mellow AM, et al.: CSF monoamine metabolites and somatostatin in Alzheimer's disease and major depression. *Biol Psychiatry* 1991; 29:1110-8.
85. Navarro JA, Molina JA, Jimenez-Jimenez FJ, Benito-Leon J, Orti-Pareja M, Gasalla T, et al.: Cerebrospinal fluid nitrate levels in patients with Alzheimer's disease. *Acta Neurol Scand* 1996; 94:411-4.
86. Nilsson CL, Brinkmalm A, Minthon L, Blennow K, Ekman R: Processing of neuropeptide Y, galanin, and somatostatin in the cerebrospinal fluid of patients with Alzheimer's disease and frontotemporal dementia. *Peptides* 2001; 22:2105-12.
87. Nyback H, Nyman H, Blomqvist G, Sjorgen I, Stone-Elander S: Brain metabolism in Alzheimer's dementia: studies of 11C-deoxyglucose accumulation, CSF monoamine metabolites and neuropsychological test performance in patients and healthy subjects. *J Neurol Neurosurg Psychiatry* 1991; 54:672-8.
88. Parnetti L, Gaiti A, Reboldi GP, Santucci C, Mecocci P, Brunetti M, et al.: CSF monoamine metabolites in old age dementias. *Mol Chem Neuropathol* 1992; 16:143-57.
89. Peskind ER, Elrod R, Dobie DJ, Pascualy M, Petrie E, Jensen C, et al.: Cerebrospinal fluid epinephrine in Alzheimer's disease and normal aging. *Neuropsychopharmacology* 1998; 19:465-71.
90. Pinessi L, Rainero I, De Gennaro T, Gentile S, Portaleone P, Bergamasco B: Biogenic amines in cerebrospinal fluid and plasma of patients with dementia of Alzheimer type. *Funct Neurol* 1987; 2:51-8.
91. Pinto T, Lanctôt KL, Herrmann N: Revisiting the cholinergic hypothesis of behavioral and psychological symptoms in dementia of the Alzheimer's type. *Ageing Res Rev* 2011; 10:404-412.
92. Pomara N, Singh RR, Deptula D, LeWitt PA, Bissette G, Stanley M, et al.: CSF corticotropin-releasing factor (CRF) in Alzheimer's disease: its relationship to severity of dementia and monoamine metabolites. *Biol Psychiatry* 1989; 26:500-4.
93. Raedler TJ & Wiedemann K: CSF-studies in neuropsychiatric disorders. *Neuro Endocrinol Lett* 2006; 7:297-305.
94. Raskind MA, Peskind ER, Holmes C, Goldstein DS: Patterns of cerebrospinal fluid catechols support increased central noradrenergic responsiveness in aging and Alzheimer's disease. *Biol Psychiatry* 1999; 46:756-65.
95. Raskind MA, Peskind ER, Lampe TH, Risse SC, Taborsky GJ Jr, Dorsa D: Cerebrospinal fluid vasopressin, oxytocin, somatostatin, and beta-endorphin in Alzheimer's disease. *Arch Gen Psychiatry* 1986; 43:382-8.
96. Reinikainen KJ, Soininen H, Riekkinen PJ: Neurotransmitter changes in Alzheimer's disease: implications to diagnostics and therapy. *J Neurosci Res* 1990; 27:576-86.

97. Rodríguez JJ, Noristani HN, Verkhatsky A: The serotonergic system in ageing and Alzheimer's disease. *Prog Neurobiol* 2012; 99:15-41.
98. Roe CM, Fagan AM, Grant EA, Holtzman DM, Morris JC: CSF biomarkers of Alzheimer disease: "noncognitive" outcomes. *Neurology* 2013; 81:2028-31.
99. Rojas-Fernandez CH, Lanctot KL, Allen DD, MacKnight C: Pharmacotherapy of behavioral and psychological symptoms of dementia: time for a different paradigm? *Pharmacotherapy* 2001; 21:74-102.
100. Rösler N, Wichart I, Jellinger KA: Ex vivo lumbar and post mortem ventricular cerebrospinal fluid substance P-immunoreactivity in Alzheimer's disease patients. *Neurosci Lett* 2001; 299:117-20.
101. Sáez-Valero J, Barquero MS, Marcos A, McLean CA, Small DH: Altered glycosylation of acetylcholinesterase in lumbar cerebrospinal fluid of patients with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2000; 69:664-7.
102. Sáez-Valero J, Fodero LR, Sjögren M, Andreasen N, Amici S, Gallai V, et al.: Glycosylation of acetylcholinesterase and butyrylcholinesterase changes as a function of the duration of Alzheimer's disease. *J Neurosci Res* 2003; 72:520-6.
103. Sáez-Valero J, Sberna G, McLean CA, Masters CL, Small DH: Glycosylation of acetylcholinesterase as diagnostic marker for Alzheimer's disease. *Lancet* 1997; 350:929.
104. Saez-Valero J & Small DH: Altered glycosylation of cerebrospinal fluid butyrylcholinesterase in Alzheimer's disease. *Brain Res* 2001; 889:247-50.
105. Samakashvili S, Ibáñez C, Simó C, Gil-Bea FJ, Winblad B, Cedazo-Minguez A, et al.: Analysis of chiral amino acids in cerebrospinal fluid samples linked to different stages of Alzheimer disease. *Electrophoresis* 2011; 32:2757-64.
106. Schliebs R & Arendt T: The cholinergic system in aging and neuronal degeneration. *Behav Brain Res* 2011; 221:555-63.
107. Shaw LM, Korecka M, Clark CM, Lee VM, Trojanowski JQ: Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov* 2007; 6:295-303.
108. Sheline YI, Miller K, Bardgett ME, Csernansky JG: Higher cerebrospinal fluid MHPG in subjects with dementia of the Alzheimer type. Relationship with cognitive dysfunction. *Am J Geriatr Psychiatry* 1998; 6:155-61.
109. Silveyra MX, García-Ayllón MS, Serra-Basante C, Mazzoni V, García-Gutierrez S, Manzanares J, et al.: Changes in acetylcholinesterase expression are associated with altered presenilin-1 levels. *Neurobiol Aging* 2012; 33:627.e27-e37.
110. Sirviö J, Kutvonen R, Soininen H, Hartikainen P, Riekkinen PJ: Cholinesterases in the cerebrospinal fluid, plasma, and erythrocytes of patients with Alzheimer's disease. *J Neural Transm* 1989; 75:119-27.
111. Sjogren M, Minthon L, Passant U, Blennow K, Wallin A: Decreased monoamine metabolites in frontotemporal dementia and Alzheimer's disease. *Neurobiol Aging* 1998; 19:379-84.
112. Smith CC, Bowen DM, Francis PT, Snowden JS, Neary D: Putative amino acid transmitters in lumbar cerebrospinal fluid of patients with histologically verified Alzheimer's dementia. *J Neurol Neurosurg Psychiatry* 1985; 48:469-71.
113. Soininen H, MacDonald E, Rekonen M, Riekkinen PJ: Homovanillic acid and 5-hydroxyindoleacetic levels in cerebrospinal fluid of patients with senile dementia of Alzheimer type. *Acta Neurol Scand* 1981; 64:101-7.
114. Steele C, Rovner B, Chase GA, Folstein M: Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am J Psychiatry* 1990; 147:1049-1051.
115. Stern Y, Tang MX, Albert MS, Brandt J, Jacobs DM, Bell K, et al.: Predicting time to nursing home care and death in individuals with Alzheimer disease. *JAMA* 1997; 277:806-12.
116. Strittmatter M, Cramer H, Reuner C, Strubel D, Hamann G, Schimrigk K: Molecular forms of somatostatin-like immunoreactivity in the cerebrospinal fluid of patients with senile dementia of the Alzheimer type. *Biol Psychiatry* 1997; 41:1124-30.
117. Stuerenburg HJ, Ganzer S, Muller-Thomsen T: 5-Hydroxyindoleacetic acid and homovanillic acid concentrations in cerebrospinal fluid in patients with Alzheimer's disease, depression and mild cognitive impairment. *Neuro Endocrinol Lett* 2004; 25:435-7.
118. Suemaru S, Hashimoto K, Ogasa T, Hirasawa R, Makino S, Ota Z, et al.: Cerebrospinal fluid and plasma corticotropin-releasing hormone in senile dementia. *Life Sci* 1991; 48:1871-9.
119. Suemaru S, Suemaru K, Hashimoto K, Ogasa T, Hirasawa R, Makino S, et al.: Cerebrospinal fluid corticotropin-releasing hormone and ACTH, and peripherally circulating choline-containing phospholipid in senile dementia. *Life Sci* 1993; 53:697-706.
120. Sunderland T, Rubinow DR, Tariot PN, Cohen RM, Newhouse PA, Mellow AM, et al.: CSF somatostatin in patients with Alzheimer's disease, older depressed patients, and age-matched control subjects. *Am J Psychiatry* 1987; 144:1313-6.
121. Tohgi H, Abe T, Hashiguchi K, Saheki M, Takahashi S: Remarkable reduction in acetylcholine concentration in the cerebrospinal fluid from patients with Alzheimer type dementia. *Neurosci Lett* 1994; 177:139-42.
122. Tohgi H, Ueno M, Abe T, Takahashi S, Nozaki Y: Concentrations of monoamines and their metabolites in the cerebrospinal fluid from patients with senile dementia of the Alzheimer type and vascular dementia of the Binswanger type. *J Neural Transm Park Dis Dement Sect* 1992; 4:69-77.
123. Trushina E, Dutta T, Persson XM, Mielke MM, Petersen RC: Identification of altered metabolic pathways in plasma and CSF in mild cognitive impairment and Alzheimer's disease using metabolomics. *PLoS One* 2013; 8:e63644.
124. Ubhi K & Masliah E: Alzheimer's disease: recent advances and future perspectives. *Alzheimers Dis* 2013; 33:S185-94.
125. van der Cammen TJ, Tiemeier H, Engelhart MJ, Fekkes D: Abnormal neurotransmitter metabolite levels in Alzheimer patients with a delirium. *Int J Geriatr Psychiatry* 2006; 21:838-43.
126. Vermeiren Y, Le Bastard N, Van Hemelrijck A, Drinkenburg WH, Engelborghs S, De Deyn PP: Behavioral correlates of cerebrospinal fluid amino acid and biogenic amine neurotransmitter alterations in dementia. *Alzheimers Dement* 2013; 9:488-98.
127. Vermeiren Y, Van Dam D, Aerts T, Engelborghs S, De Deyn PP: Brain region-specific monoaminergic corre-

- lates of neuropsychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis* 2014a; 41:819-33.
128. Vermeiren Y, Van Dam D, Aerts T, Engelborghs S, De Deyn PP: Monoaminergic neurotransmitter alterations in postmortem brain regions of depressed and aggressive patients with Alzheimer's disease. *Neurobiol Aging* 2014b; S0197-4580(14)00397-2.
129. Volicer L, Direnfeld LK, Langlais PJ, Freedman M, Bird ED, Albert ML: Catecholamine metabolites and cyclic nucleotides in cerebrospinal fluid in dementia of Alzheimer type. *J Gerontol* 1985b; 40:708-13.
130. Volicer L, Langlais PJ, Matson WR, Mark KA, Gamache PH: Serotonergic system in dementia of the Alzheimer type. Abnormal forms of 5-hydroxytryptophan and serotonin in cerebrospinal fluid. *Arch Neurol* 1985a; 42:1158-61.
131. Wenk GL, Parsons CG, Danysz W: Potential role of N-methyl-D-aspartate receptors as executors of neurodegeneration resulting from diverse insults: focus on memantine. *Behav Pharmacol* 2006; 17:411-424.
132. Wester P, Eriksson S, Forsell A, Puu G, Adolfsson R: Monoamine metabolite concentrations and cholinesterase activities in cerebrospinal fluid of progressive dementia patients: relation to clinical parameters. *Acta Neurol Scand* 1988; 77:12-21.
133. Wuwongse S, Chang RC, Law AC: The putative neurodegenerative links between depression and Alzheimer's disease. *Prog Neurobiol* 2010; 91:362-75.
134. Xu Y, Yan J, Zhou P, Li J, Gao H, Xia Y, Wang Q: Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease. *Prog Neurobiol* 2012; 97:1-13.
135. Yasuda M, Maeda K, Kakigi T, Minamitani N, Kawaguchi T, Tanaka C: Low cerebrospinal fluid concentrations of peptide histidine valine and somatostatin-28 in Alzheimer's disease: altered processing of prepro-vasoactive intestinal peptide and prepro-somatostatin. *Neuropeptides* 1995; 29:325-30.
136. Yeh YC & Ouyang WC: Mood stabilizers for the treatment of behavioral and psychological symptoms of dementia: An update review. *Kaohsiung J Med Sci* 2012; 28:185-193.
137. Zetterberg H & Blennow K: Cerebrospinal Fluid Biomarkers for Alzheimer's Disease: More to Come? *J Alzheimers Dis* 2013; 33:361-69.
138. Zimmer R, Teelken AW, Trieling WB, Weber W, Weihmayr T, Lauter H: Gamma-aminobutyric acid and homovanillic acid concentration in the CSF of patients with senile dementia of Alzheimer's type. *Arch Neurol* 1984; 41:602-4.
139. Zubenko GS, Marquis JK, Volicer L, Direnfeld LK, Langlais PJ, Nixon RA: Cerebrospinal fluid levels of angiotensin-converting enzyme, acetylcholinesterase, and dopamine metabolites in dementia associated with Alzheimer's disease and Parkinson's disease: a correlative study. *Biol Psychiatry* 1986; 21:1365-81.

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