Assessment of Cerebrospinal Fluid (CSF) β-Amyloid (1-42), Phosphorylated Tau (ptau-181) and Total Tau Protein in Patients with Alzheimer's Disease (AD) and Other Dementia at Siriraj Hospital, Thailand

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Background : *The combination of decreased cerebrospinal fluid (CSF) levels of β-amyloid (1-42) and increased levels of phosphorylated tau (ptau-181) or total tau protein are known to be biomarkers of Alzheimer's disease (AD). These biomarkers can also be used as predictors of disease progression in persons with mild cognitive impairment. Utilizing biomarkers to differentiate Alzheimer's disease (AD) against non-Alzheimer dementia (non-AD) needs to be explored.*
Objective: *To evaluate the clinical use of CSF biomarker: β-amyloid (1-42), phosphorylated tau (ptau-181) and total tau protein for distinguishing Alzheimer's disease (AD) from non-Alzheimer dementia (non-AD) in Thai patients.*
Material and Method: *Thirty patients diagnosed of dementia during 2005-2007 at Siriraj hospital were offered CSF analysis for β-amyloid (1-42), phosphorylated tau (ptau-181) and total tau protein. Diagnosis of dementia was performed by a concensus diagnostic group utilizing a standard criteria for diagnosis of AD and other dementia. All CSF testing was performed by Enzyme-Linked Immunoassay (ELISA) technique of the INNOTEST™ to analyze these biomarkers.*
Results: *Thirty demented patients were recruited in the study. Fourteen had AD and 16 had non-AD including 5 vascular dementia, 5 normal pressure hydrocephalus, 4 frontotemporal lobar degeneration and others. Mean age of the AD group was 67.79 (12.30) and that of non-AD group was 65.75 (15.04). Twelve AD had decreased levels of CSF β-amyloid (1-42) (less than 487 pg/ml). Only one patient with AD had increased CSF phosphorylated tau (ptau-181) (more than 61 pg/ml). None of the AD patient had increased CSF total tau (more than 425 pg/ml). Eight patients with non-AD had decreased levels of CSF β-amyloid (1-42), one had increased CSF total tau protein, and none had increased CSF phosphorylated tau (ptau-181) protein. The sensitivity of decreased level of CSF β-amyloid (1-42) in AD against non-AD dementia was 85.71%. Those of increased CSF total tau and phosphorylated tau (ptau-181) protein in AD against non-AD dementia were 7.14% and 0% consecutively. The specificity of decreased level of CSF β-amyloid (1-42) in AD against non-AD dementia was 50%. The specificity of increased CSF total tau and phosphorylated tau (ptau-181) protein in AD against non-AD dementia were 100% and 93.75% sequentially. The combination of 2 biomarkers would increase specificity but decrease sensitivity.*
Conclusion: *CSF biomarker analysis should be encouraged to use as diagnostic aid in memory clinic especially to help diagnosis of atypical presentation of AD. The usefulness of longitudinal data needs to be explored.*

Keywords: *CSF β-amyloid (1-42), CSF phosphorylated tau (ptau-181), CSF total tau protein, Alzheimer's disease, non-Alzheimer dementia*

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Both β-amyloid and Tau protein have an intimate relation to two different hallmarks of neuropathologic feature of AD: senile plaques and neurofibrillary tangles, respectively[1-3]. The amyloid cascade hypothesis implicates β-amyloid as necessary in the pathogenesis of Alzheimer's disease and measurement of β-amyloid (1-42) in the CSF is likely to provide insight into CNS β-amyloid (1-42) metabolism including in production and clearance of CNS β-amyloid[4,5]. Neurofibrillary tangles are formed by hyperphosphorylation of tau protein, causing it to aggregate in an insoluble form referred to as intracellular Paired Helical Filaments[3,6]. Increased levels of CSF tau, probably as a consequence of neuronal/axonal damage, have been reported mainly in AD and other neuronal disease including Creutzfeldt-Jakob disease, stroke, Progressive Supranuclear Palsy and also normal aging brain[3,6]. The previous study shows that decreased CSF levels of β-amyloid (1-42) are known to be biomarkers of Alzheimer's disease and the combination of decreased CSF levels of β-amyloid (1-42) and increased levels of phosphorylated tau (ptau-181) or total tau protein can increase in sensitivity and specificity for diagnostic marker of Alzheimer's disease[7,8]. These biomarkers can be not only used as diagnostic tool in Alzheimer disease particular but predictors of disease conversion in persons with mild cognitive impairment[9,10,21,31,32]. This study is the first report in Thai patients using laboratory analysis of CSF biomarkers in dementia. We explored the clinical use of CSF biomarkers in discriminating Alzheimer's disease (AD) from non-Alzheimer dementia (non-AD).

Material and Method

Subjects

Thirty patients diagnosed of dementia during 2005-2007 at Siriraj hospital. 14 had AD and 16 had non-AD including 5 vascular dementia, 5 normal pressure hydrocephalus, 4 frontotemporal lobar degeneration and 2 dementia from psychiatric disorders. All were offered to have CSF analysis for β-amyloid (1-42), phosphorylated tau (ptau-181) and total tau protein. Diagnosis of dementia was performed by a concensus diagnostic group utilizing a standard criteria for diagnosis of AD and other dementia[11]. Most patients were diagnosed and follow-up in memory clinic, Division of Neurology, Department of Medicine, Siriraj hospital. AD and non-AD group was determined in case and control group for this study to assess the clinical use of CSF biomarkers in discriminating AD from non-AD patient. This study was approved by ethical committee at Faculty of Medicine, Siriraj Hospital, Mahidol University.

CSF analysis

CSF was obtained by lumbar puncture between the L3 and L4 or L4 and L5 intervertebral space after an informed consent by patients or relatives. A small amount of CSF was used for routine analysis, including total cell count, differential WBC count, total protein and sugar. Some CSF was aliquoted in polypropylene tubes of 0.5 or 1 mL and stored at -80°C until analysis. All CSF samples had undergone a freeze-thaw cycle before analytic process within 6 months[7,12]. CSF β-amyloid (1-42), CSF phosphorylated tau (ptau-181) and CSF total tau protein were measured by commercially available Enzyme-Linked Immunoassay (ELISA) technique of the INNOTEST™ (the INNOTEST™ for β-amyloid (1-42), phospho-tau (ptau-181) and t-tau Ag; Innogenetics, Ghent, Belgium)[7,12]. Prior studies have indicated that biomarker levels remain stable in AD individuals when CSF samples are compared over an average interval of 10-18 months[15,16]. All CSF analytic methods were performed at the Division of Neurology, Department of Medicine, Siriraj hospital. The cut-off value of CSF β-amyloid (1-42) (less than 487 pg/ml), CSF phosphory-lated tau (ptau-181) (more than 61 pg/ml) and CSF total tau protein (more than 425 pg/ml) were obtained by Innogenetics and previous studies[7,8,13,14].

Statistical analysis

The analysis of the CSF levels was determined in case-control study between 2 groups; AD as a case and non-AD as a control group. Age, gender, cognitive assessment (Thai Mental State Examination (TMSE) score) and mean CSF biomarker level was shown in comparison. Decreased levels of CSF β-amyloid (1-42) less than 487 pg/ml, increased CSF phosphorylated tau (ptau-181) more than 61 pg/ml or increased CSF total tau more than 425 pg/ml were categorized to support the diagnosis of AD and the opposite data was against[7,8]. CSF biomarker levels were evaluated to calculate the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) from multiple two by two tables. And the combined test of CSF β-amyloid (1-42) levels and tau levels were assessed in the same method.

Results

Thirty demented patients were recruited in the study. Fourteen had AD and 16 had non-AD including

5 vascular dementia, 5 normal pressure hydrocephalus, 4 frontotemporal lobar degeneration and 2 others. Mean age of the AD group was 67.79 ± 12.30 and that of non-AD group was 65.75 ± 15.04. Gender, cognitive score (TMSE) and mean CSF biomarker level was shown in Table 1 patient characteristics. Mean CSF Aβ (1-42) levels in AD was 310.82 ± 121.13 pg/ml as well as non-AD 421.71 ± 245.62 pg/ml with mean difference of 110.89 pg/ml. And mean CSF ptau-181 and total tau were 18.81 ± 22.93 and 119.57 ± 67.88 pg/ml in AD as well as 3.28 ± 2.61 and 185.57 ± 316.23 in non-AD respectively.

Twelve AD had decreased levels of CSF β-amyloid (1-42) (less than 487 pg/ml). Only one patient with AD had increased CSF phosphorylated tau (ptau-181) (more than 61 pg/ml). None of the AD patient had increased CSF total tau (more than 425 pg/ml). Eight patients with non-AD had decreased levels of CSF β-amyloid (1-42), one had increased CSF total tau protein, and none had increased CSF phosphorylated tau (ptau-181) protein. The sensitivity of decreased level of CSF β-amyloid (1-42) in AD against non-AD dementia was 85.71%. Those of increased CSF total tau and phosphorylated tau (ptau-181) protein in AD against non-AD dementia were 7.14% and 0% consecutively. The specificity of decreased level of CSF β-amyloid (1-42) in AD against non-AD dementia was 50%. The specificity of increased CSF total tau and phosphorylated tau (ptau-181) protein in AD against non-AD dementia were 100% and 93.75% sequentially. The combination of 2 biomarkers would increase specificity but decrease sensitivity.

Discussion

Twelve (85.71%) from 14 AD patients had low level of CSF Aβ (1-42). Mean CSF Aβ (1-42) levels in AD is 310.82 ± 121.13 pg/ml as well as non-AD 421.71 ± 245.62 pg/ml with mean difference of 110.89 pg/ml. And cross tabulation of CSF Aβ (1-42 represent good sensitivity (85.71%) and specificity (50%) to differentiate AD from non-AD patient. The normal range (125-2,000 pg/ml) and cut-off value (487 pg/ml) of CSF Aβ (1-42) level were applied and calculated to sensitivity (85.71%), specificity (50%), NPV (80%), PPV (60%), positive likelihood ratio (sensitivity/(1-specificity) = 1.71) and negative likelihood ratio ((1-sensitivity)/specificity = 0.28). Our results reflect the similarity with previous knowledge about CSF Aβ (1-42) and could be correlated with CNS β-amyloid metabolism. Numerous studies have documented the changes of CSF Aβ (1-42) in AD patient and the decreased level of CSF Aβ (1-42) could be useful in improving the diagnosis of AD[7,19,20] .

Low CSF Aβ (1-42) level in AD against non-AD has good sensitivity (85.71%) and specificity (50%). High CSF ptau-181 or total tau level and the combined test can increase in specificity but has low sensitivity. Our results are the first report of CSF biomarkers in Thailand. It is hard to determined the exact normal range and cut-off value of CSF biomarkers level because many variable factors can change the numerical data, particularly cut-off values such as race, disease stage, timing of samples and the analytical process, including control sample, QC sample, technical error and laboratory standardization[7]. The knowledge about fluctuation of CSF Aβ (1-42) level 1.5 to fourfold was detected over 36 hours of serially sampling in individual subjects, thus CSF sampling time difference can increase variability[22]. The results from various laboratories still have no consensus in clinical application for appropriate level of CSF Aβ (1-42), especially in different population. Several studies of CSF in AD patients have used different methods and nomenclature for assessing and describing CSF Aβ (1-42) level[7,13,23,24]. The biomarkers data comparison from different laboratories is difficult to interpret, but the similarity of outcomes can improve the validity[7].

Only one AD has high CSF ptau-181 and 1 non-AD has high total tau level. The low CSF ptau-181 or total tau level in our study requires more investigation. In several previous studies, CSF tau is increased to around 300% of control concentration in AD, probably as result of neuronal and axonal degeneration[19,20]. Our study investigated the difference in CSF biomarkers level in AD against non-AD, with no normally cognitive control subject. But the low CSF ptau-181 or total tau level may come either from laboratory variations or from having no data comparison among the non-demented controls. Therefore investigation between demented and non-demented person may assist the true normal range and cut-off value of the CSF level and can improve the validation of our data. And additional studies are required to establish methodologic standardization in the CSF assays across laboratory centers.

The combined measurement of CSF Aβ (1-42) and tau level meets the requirement for clinical use in discriminating AD from normal aging and specific neurologic disorders and was proved in previous studies[7,13,24]. And both β-amyloid (1-42) and tau protein are closely related to the pathognomonic features of amyloid plaques and neurofibrillary tangles in AD brain[1-3]. The combination of 2 biomarkers in our study

Table 1. Patient characteristics

	Alzheimer's disease (AD)	non-Alzheimer dementia (non-AD)
Number (diagnosis)	14	16 (5 VaD, 5 NPH, 4 FTD, 2 other)
Age (years)	67.79 ± 12.30	65.75 ± 15.04
Female : male	9: 5	8: 7
TMSE score	16.82 ± 8.57	13.64 ± 6.70
Mean CSF β-amyloid (1-42) (pg/ml)	310.82 ± 121.13 (n = 12)	421.71 ± 245.62 (n = 16)
Mean CSF ptau-181 (pg/ml)	18.81 ± 22.93 (n = 12)	3.28 ± 2.61 (n = 16)
Mean CSF total tau (pg/ml)	119.57 ± 67.88 (n = 6)	185.57 ± 316.23 (n = 5)

Table 2. Cross tabulation of CSF Aβ (1-42), ptau-181 and total tau protein in AD and non-AD group

	AD n = 14	non-AD n = 16	sensitivity	specificity	PPV	NPV
1. β-amyloid (1-42) ≤ 487 pg/ml	12	8	85.71%	50%	60%	80%
β-amyloid (1-42) > 487 pg/ml	2	8				
2. ptau-181 ≥ 61 pg/ml	1	0	7.14%	100%	100%	55.17%
ptau-181 < 61 pg/ml	13	16				
3. total tau ≥ 425 pg/ml	0	1	0%	93.75	0%	51.72%
total tau < 425 pg/ml	14	15				

Table 3. The combined test

	AD n = 14	non-AD n = 16	sensitivity	specificity	PPV	NPV
1. combination of β-amyloid (1-42) ≤ 487 and ptau-181 ≥ 61 pg/ml						
Positive test	1	0	7.14%	100%	100%	55.17%
Negative test	13	16				
2. Combination of β-amyloid (1-42) ≤ 487 and total tau ≥ 425 pg/ml						
Positive test	0	0	0%	100%	-	53.33%
Negative test	14	14				

(Table 3) would increase specificity but decrease sensitivity in diagnosis of AD against non-AD. To justify the clinical use of the combination as a diagnostic aid in memory clinic particularly of atypical presentation of AD, usefulness of longitudinal data in CSF biomarker analysis should be explored in every clinic.

An ideal biomarker should have a sensitivity of ≥ 80% in detecting AD and a specificity of ≥ 80% for distinguishing from other dementias[18]. In comparison with previous studies, six large prospective studies in decreased CSF β-amyloid (1-42) level in AD represent a mean sensitivity of 89%, with a specificity of 90% against cognitively normal elderly people[7,19,20] but a few data present, call for comparison against the non-AD group. And many reports have shown that the addition of CSF phosphorylated tau increases the ability to differentiate AD from other dementias, reaching specific figures of above 80%[20,21].

Conclusion

Various tools including magnetic resonance imaging (MRI) measurements of medial temporal atrophy, positron emission topography (PET) imaging of glucose metabolism, Aβ deposits and CSF biomarkers

were developed to aid the diagnosis of Alzheimer's disease. CSF biomarker analysis is also emerging as an advantageous tool. The search for CSF biomarkers focused on β-amyloid (1-42) and tau protein represent the effectiveness in diagnosis. Utilization of CSF biomarkers should be encouraged as a diagnostic aid in memory clinic, especially in cases of atypical presentation of AD.

Potential conflicts of interest

None.

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การศึกษาประเมินผลระดับสาร beta-amyloid (1-42), phosphorylated tau (ptau-181) และ total tau protein ในน้ำไขสันหลังของผู้ป่วยโรคสมองเสื่อมชนิดอัลไซเมอร์ เปรียบเทียบกับผู้ป่วยโรคสมองเสื่อมชนิดอื่น ๆ ในโรงพยาบาลศิริราช

เจษฎา ทวีโภคสมบูรณ์, วรพรรณ เสนาณรงค์, นิพนธ์ พวงวรินทร์, ทิพา ชาคร, นบวรรณ ศิวะศริยานนท์, เลิศชาย วชิรุตมางกูร, สุทธิพล อุดมพันธุรัก

ภูมิหลัง: *การลดลงของระดับสาร beta-amyloid (1-42) ร่วมกับการเพิ่มขึ้นของระดับสาร phosphorylated tau (ptau-181) หรือ total tau protein ในน้ำไขสันหลังของผู้ป่วยโรคสมองเสื่อม ถือเป็นตัวบ่งชี้อย่างหนึ่งที่ช่วยสนับสนุนการวินิจฉัยโรคสมองเสื่อมชนิดอัลไซเมอร์ แยกออกจากโรคสมองเสื่อมชนิดอื่น รวมทั้งระดับของโปรตีนดังกล่าวในน้ำไขสันหลังยังสามารถช่วยพยากรณ์โรคในผู้ป่วยที่เป็น MCI (Mild cognitive impairment) ว่าจะมีการดำเนินโรคเป็นอัลไซเมอร์ต่อไปในอนาคตหรือไม่ แต่ประโยชน์และการนำไปใช้ทางคลินิกเพื่อวินิจฉัยแยกโรคสมองเสื่อมชนิดอัลไซเมอร์ยังต้องการการศึกษาเพิ่มเติม*

วัตถุประสงค์: *ศึกษาถึงประโยชน์และการนำไปใช้ทางคลินิกของการตรวจวัดระดับสาร beta-amyloid (1-42), phosphorylated tau (ptau-181) และ total tau protein ในน้ำไขสันหลังเพื่อช่วยวินิจฉัยแยกโรคสมองเสื่อมชนิดอัลไซเมอร์ ออกจากโรคสมองเสื่อมชนิดอื่น*

วัสดุและวิธีการ: *การตรวจน้ำไขสันหลังในผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคสมองเสื่อม ในช่วงปี พ.ศ. 2548 ถึง พ.ศ. 2550 ในโรงพยาบาลศิริราช ทั้งหมด 30 คน การวินิจฉัยโรคสมองเสื่อมโดย a concensus diagnostic group utilizing a standard criteria for diagnosis of AD and other dementia แบ่งชนิดของผู้ป่วยเป็นกลุ่มที่เป็น โรคสมองเสื่อมชนิดอัลไซเมอร์ และกลุ่มโรคสมองเสื่อมชนิดอื่น ซึ่งน้ำไขสันหลังทั้งหมดจะถูกส่งตรวจด้วยวิธี enzyme-linked immunoassay (ELISA) technique ของบริษัท the INNOTEST™*

ผลการศึกษา: *น้ำไขสันหลังของผู้ป่วยทั้งหมด 30 คนแบ่งเป็นผู้ป่วยโรคสมองเสื่อมชนิดอัลไซเมอร์ 14 คน และเป็นโรคสมองเสื่อมชนิดอื่น 16 คน ได้แก่ โรคสมองเสื่อมชนิด vascular dementia 5 คน, normal pressure hydrocephalus 5 คน, frontotemporal lobar degeneration 4 คน และชนิดอื่น ๆ อีก 2 คน อายุเฉลี่ยของกลุ่มผู้ป่วย กลุ่มอัลไซเมอร์ 67.79 (12.30) ปี และกลุ่มสมองเสื่อมชนิดอื่น 65.75 (15.04) ปี ผู้ป่วยอัลไซเมอร์ 12 คน ตรวจพบว่า มีการลดลงของระดับสาร beta-amyloid (1-42) และมีเพียง 1 คน ในกลุ่มผู้ป่วยอัลไซเมอร์ที่ตรวจพบมีการเพิ่มขึ้น ของระดับสาร phosphorylated tau (ptau-181) ไม่พบการเพิ่มขึ้นของระดับสาร total tau protein ในผู้ป่วยอัลไซเมอร์เลย ผู้ป่วยสมองเสื่อมชนิดอื่น มีการตรวจพบว่า 8 คน มีการลดลงของระดับสาร beta-amyloid (1-42) มี 1 คน พบการเพิ่มขึ้นของระดับสาร total tau protein และไม่พบการเพิ่มขึ้นของระดับสาร phosphorylated tau (ptau-181) ในผู้ป่วยโรคสมองเสื่อมชนิดอื่นเลย การคำนวณความไว (sensitivity) และความจำเพาะ (specificity) ของการทดสอบการลดลงของระดับสาร beta-amyloid (1-42) ในผู้ป่วยอัลไซเมอร์พบว่าความไวเท่ากับ 85.71% ความจำเพาะเท่ากับ 50% การคำนวณความไวของการทดสอบ การเพิ่มขึ้นของระดับสาร total tau protein และ phosphorylated tau (ptau-181) พบว่าความไวเท่ากับ 7.14% และ 0% ตามลำดับแต่การคำนวณความจำเพาะของการ ทดสอบนี้ได้เท่ากับ 100% และ 93.75% ตามลำดับ ถ้านำการทดสอบทั้งสองคือ การลดลงของระดับสาร beta-amyloid (1-42) ร่วมกับการเพิ่มขึ้นของระดับสาร phosphorylated tau (ptau-181) หรือ total tau protein จะพบว่า สามารถเพิ่มความจำเพาะของการทดสอบได้ แต่ความไวของการทดสอบจะลดลง*

สรุป: *การวัดระดับโปรตีนในน้ำไขสันหลังดังกล่าว ถือเป็นตัวบ่งชี้อย่างหนึ่งในการวินิจฉัยผู้ป่วยสมองเสื่อม ชนิดอัลไซเมอร์ โดยเฉพาะอย่างยิ่งช่วยในการวินิจฉัยในกลุ่มผู้ป่วยที่มาด้วยอาการไม่เฉพาะเจาะจงและวินิจฉัยได้ยาก แต่ประโยชน์และการนำไปใช้ทางคลินิกยังต้องอาศัยการศึกษาเพิ่มเติมในอนาคต*