Review Article

α-Synuclein as CSF and Blood Biomarker of Dementia with Lewy Bodies

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1. Introduction

Dementia with Lewy bodies (DLB) is a common subtype of dementia in the elderly. DLB is neuropathologically characterized by the presence of Lewy bodies and Lewy neurites, both of which are composed of α-synuclein. Although α-synuclein was initially considered to be an exclusively intracellular protein, it has been found to be secreted into biological fluids. α-Synuclein in biological fluids such as cerebrospinal fluid (CSF) and blood has been discussed as a potential biomarker of DLB and α-synuclein-related disorders, because α-synuclein is characteristically accumulated in the brain of patients with these disorders. The α-synuclein level in CSF has been examined by several investigators, and the majority of studies have shown a reduction in CSF α-synuclein level in DLB and α-synuclein-related disorders. Discrepant findings of studies of plasma α-synuclein level in patients with DLB have been reported. Because the level of α-synuclein stored in red blood cells is considerably high, blood contamination and haemolysis during sample collection and processing should be considered as a confounding factor for quantification of α-synuclein. Here, the recent progress in the studies of α-synuclein as a biomarker of DLB and their potential clinical applications are reviewed.
Tretiakov, named the inclusions as “corps de Lewy (Lewy bodies)” [12]. Since the discovery, Lewy bodies have been considered as intracytoplasmic, spherical, and eosinophilic neuronal inclusions in the substantia nigra of PD patients. In 1976, Kosaka et al. reported the detection of Lewy bodies in the cerebral cortex of an elderly patient with dementia [13]. A year after Spillantini et al. reported that α-synuclein in families with autosomal dominant PD [17]. A different SNCA mutation was subsequently reported in a family with DLB [18]. In addition, SNCA multiplication by duplication/triplication has been identified in a large family with phenotypes ranging from DLB to PD [19]. These neuropathological and genetic findings suggest that α-synuclein is essentially implicated in the pathogenesis of LBD including DLB and PD. Recent studies have suggested that the Lewy body pathology propagates throughout the brain via neuronal-to-neuron transmission of α-synuclein aggregates [20]. It has been demonstrated that glial cytoplasmic inclusions, which are unique pathological inclusions found in brains of patients with multiple system atrophy (MSA), are also composed of α-synuclein [21], suggesting an unexpected link between MSA and LBD. These disorders with pathological accumulation of α-synuclein in brains are termed as α-synucleinopathies [22].

α-Synuclein is a 140-residue ubiquituous protein and is highly expressed in neuronal presynaptic terminals under physiological conditions. Although its physiological functions remain unclear, α-synuclein is implicated in synaptic vesicle trafficking particularly in the regulation of synaptic vesicle release [23] and stabilization of SNARE complexes [24]. Deposited α-synuclein in the brain with synucleinopathies is aberrantly phosphorylated at Ser129 [25]. It has been demonstrated that the C-terminal truncated form of α-synuclein promotes the aggregation of α-synuclein [26]. Because α-synuclein has no signal sequence, it was initially considered to be an exclusively intracellular protein. However, it has been shown that α-synuclein is secreted into biological fluids [27, 28].

3. α-Synuclein in CSF

A year after Spillantini et al. reported that α-synuclein is the main component of Lewy bodies, Jakowec et al. examined whether α-synuclein is detectable in CSF [29]. They examined the expression of α-synuclein in CSF from PD patients and control subjects by Western blot analysis using an anti-α-synuclein specific antibody, but failed to detect α-synuclein in CSF [29]. Borghi et al. detected α-synuclein by a method combining immunoprecipitation with immunoblot analysis using two different anti-α-synuclein antibodies [30]. In their study, however, the intensity of the bands immunoreactive to the anti-α-synuclein antibodies showed no significant difference between patients with PD and control subjects [30]. El-Agnaf et al. also confirmed that α-synuclein is detectable in CSF by a similar methodology [27].

Subsequently, Tokuda et al. demonstrated using a new system for enzyme-linked immunosorbent assay (ELISA) that PD patients showed significantly lower α-synuclein levels in CSF than the control groups [31]. Since then, several studies to determine the total α-synuclein level in CSF have been carried out by ELISA or bead-based flow cytometric assay using various combinations of anti-α-synuclein antibodies (Tables 1 and 2). A significantly low level of α-synuclein in CSF from patients with LBD (PD and/or DLB) has been shown by independent studies [28, 31–38]. Our study revealed that total CSF α-synuclein level shows a significant positive correlation with the CSF Aβ42 level in DLB patients [32]. It has been suggested that a low CSF Aβ42 level may be related to amyloid-related pathology in the brains of DLB patients [39]. In addition, experimental studies have suggested that the Aβ42 species strongly enhances the accumulation of α-synuclein [40]. In the CSF from LBD patients, the level of Aβ42 shows a positive correlation with the activity of neprilysin, an enzyme that degrades Aβ [41]. Taken together, the reduction in α-synuclein and Aβ42 levels in CSF suggests the extent of Lewy body pathology and the co-occurrence of amyloid pathology, respectively, in the brain of DLB patients. Interestingly, patients with SNCA duplication who showed abundant Lewy body pathology in the brain [42] also show low levels of CSF α-synuclein [32]. Because the predominant source of α-synuclein in CSF is considered to be the central nervous system [43], the decrease in the level of CSF α-synuclein in DLB may reflect a dysfunction in the metabolism or clearance of α-synuclein in the brain, similarly to AD patients with Aβ accumulation in the brain showing a decrease in the level of Aβ42 in CSF.

In contrast, comparable levels of total α-synuclein in CSF between patients with LBD and control subjects have also been reported [45–50]. This discrepancy is probably not due to the misdiagnosis of LBD, because different studies using CSF samples derived from autopsy-confirmed patients showed significantly decreased or comparable α-synuclein levels in LBD patients [34, 50]. In addition to methodological differences in the quantification of α-synuclein, blood contamination of CSF during lumbar puncture should be taken into account when considering the discrepant results. The level of α-synuclein in blood, particularly that stored in red blood cells, is much higher than that in CSF [33, 53]. Haemolysis in the course of sample collection and processing should be considered as a confounding factor for quantification of α-synuclein level in CSF and blood. Other factors such as level fluctuations over time and drug treatment may have less effect on the level of α-synuclein in CSF. Although the level of Aβ in CSF fluctuates over time [54], the level of α-synuclein in CSF does not significantly change [52]. It is also reported that drugs such as L-dopa and dopamine agonists do not affect the level of α-synuclein in CSF [34, 35].
| Level of total α-synuclein | Study | Blood contamination was considered | Controls | AD | Synucleinopathies | Results |
|---------------------------|-------|-----------------------------------|----------|----|-------------------|---------|
|                           |       |                                    | Healthy controls | Neurological controls | Lewy body diseases | PD | MSA |
|                           |       |                                    |           |     |                   |         |
|                           |       |                                    |           |     |                   |         |
|                           |       |                                    |           |     |                   |         |
|                           |       |                                    |           |     |                   |         |
| Tokuda et al. [31]        | No    | 9                                 | 29        | —  | 33                | —       |
|                           |       |                                    |           |     |                   |         |
| Tokuda et al. [31]        | No    | 16                                | 12        | —  | 32                | —       |
| Mollenhauer et al. [28]   | No    | —                                 | 13        | 13 | 38                | 8       |
| Kasuga et al. [32]        | No    | —                                 | 21        | 31 | 34                | —       |
| Mollenhauer et al. [44]   | No    | 16                                | 12        | —  | 32                | —       |
| Mollenhauer et al. [34]   | Yes   | —                                 | 76        | 62 | 55                | 51      |
|                           |       |                                    |           |     |                   |         |
| Mollenhauer et al. [34]   | Yes   | —                                 | 20        | 3  | 66                | 273     |
|                           |       |                                    |           |     |                   |         |
| Hong et al. [33]          | Yes   | 92                                | —         | 38 | —                 | 86      |
|                           |       |                                    |           |     |                   |         |
| Parnetti et al. [37]      | Yes   | —                                 | 32        | 48 | 32                | 38      |
|                           |       |                                    |           |     |                   |         |
| Tateno et al. [36]        | No    | —                                 | 11        | 6  | 11                | 11      |
|Wennstrom et al. [38]      | No    | 24                                | —         | 26 | 18                | —       |
**Table 1: Continued.**

| Study                        | Blood contamination was considered | Controls | AD | Synucleinopathies | Results                                                                                                                                 |
|------------------------------|-----------------------------------|----------|----|-------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Ohrfelt et al. [45]          | Yes                               | 55       | 66 | 15                | PD, DLB patients and controls showed comparable levels of α-syn. AD patients showed significantly lower level of α-syn than the controls (P < 0.001). AD patients with MMSE scores below 20 had significantly lower level of α-syn than AD patients with MMSE scores of 20 or higher (P = 0.02). The level of α-syn did not differ between DLB and AD patients. In DLB patients, the duration of illness was associated with lower level of α-syn (P < 0.05). |
| Noguchi-Shinohara et al. [46]| No                                | —        | 21 | 16                | The level of α-syn was comparable between DLB, AD, and controls. The level of α-syn decreased with age (P = 0.001).                       |
| Spies et al. [47]            | No                                | 57       | 131| 40                | The level of α-syn was not different among PD, DLB, AD, and controls. In DLB patients, lower α-syn was related to lower MMSE scores (P < 0.05) and worse category fluency (P < 0.05). |
| Reesink et al. [48]          | Yes                               | 34       | 63 | 35                | The level of α-syn was comparable among PD, MSA, DLB patients and controls. In PD group, the level of α-syn was negatively correlated with age at time of lumbar puncture (P < 0.006). |
| Aerts et al. [49]            | Yes                               | 57       | 3  | 58                | The level of total α-syn was not different between PD, DLB, MSA and control groups. Oligomeric phosphorylated α-syn was significantly high in patients with MSA (P < 0.001). The level of total α-syn in PD patients was comparable to that of control groups. The level of α-syn oligomer in PD patients was significantly higher than controls (P = 0.005). |
| Foulds et al. [50]           | Yes                               | 20       | 16 | 38                | The level of total α-syn was not different between PD, DLB, MSA and control groups. Oligomeric phosphorylated α-syn was significantly high in patients with MSA (P < 0.001). |
| Park et al. [51]             | No                                | 18       | 11 | 23                | The level of total α-syn in PD patients was comparable to that of control groups. The level of α-syn oligomer in PD patients was significantly higher than controls (P = 0.005). |

Arrows indicate decreased (↓) and comparable (→) levels α-synuclein. Sample numbers are shown in each category. *Erythrocyte counts or haemoglobin levels were considered as a confounding factor. AD: Alzheimer’s disease; DLB: dementia with Lewy bodies; PD: Parkinson’s disease; MSA: multiple system atrophy; α-syn: α-synuclein; MMSE: minimental state examination.
Several groups have recently conducted studies to detect the oligomeric forms of α-synuclein in CSF, because the oligomer species of α-synuclein are considered to be toxic and could enhance pathological accumulation of α-synuclein and disease propagation [55]. Tokuda et al. demonstrated that the levels of α-synuclein oligomers in CSF are significantly higher in patients with PD than in patients with progressive supranuclear palsy (PSP) or AD [44]. In their study, the level of total α-synuclein in the CSF from PD patients tends to decrease [44]. Increased level of α-synuclein oligomers in CSF from PD patients was also shown by other investigator [51]. Foulds et al. showed that the level of oligomers composed of phosphorylated α-synuclein is higher in the postmortem CSF from MSA patients than in that from with PD, DLB, or PSP patients [50]. Sierks et al. also showed a significant increase in the level of α-synuclein oligomers in postmortem CSF from patients with PD by electrochemical impedance spectroscopy [56]. These findings suggest a possibility that α-synuclein oligomer species are detectable in CSF and that their levels may increase in some patients with synucleinopathies. A potential concern is that the oligomeric forms of α-synuclein detected in their studies using different methods may be heterogeneous in size and toxicity; hence, further validation is still needed.

Correlation analysis of clinical parameters, such as minimental state examination (MMSE) and Hoehn Yahr scale scores with the total α-synuclein level in CSF, has shown inconsistent results. Tokuda et al. showed an inverse correlation between the total α-synuclein level in CSF and disease severity determined by the Hoehn Yahr scale [31]. A low α-synuclein level was reported to correlate with a low MMSE score of DLB patients [48]. These findings suggest that α-synuclein level in CSF may reflect the severity of pathological changes occurring in patients with LBD. This notion is supported by the findings of a study that the disease duration in patients with DLB is closely associated with a low α-synuclein level in CSF [46]. In contrast to these findings, other studies revealed no significant association of the α-synuclein level in CSF with MMSE score, gender, age at examination, or disease duration in DLB or AD patients [32]. Shi et al. examined whether CSF α-synuclein level correlates with dopaminergic dysfunction determined by PET in asymptomatic carriers with leucine-rich repeat kinase 2 (LRRK2) gene mutation [64]. They detected no significant

| Study                          | Target molecule | Study                          | Target molecule | Anti-α-synuclein antibodies | Capture antibody | Detecting antibody |
|-------------------------------|-----------------|-------------------------------|-----------------|-----------------------------|------------------|-------------------|
| Tokuda et al. [31]            | Total α-synuclein | Mollenhouer et al. [28]      | Total α-synuclein | Syn1b (m)                   | Syn3b (m), Syn5d (m) |
| Noguchi-Shinohara et al. [46] | Total α-synuclein | Spies et al. [32]             | Total α-synuclein | Syn1b (m)                   | Syn3b (m), Syn5d (m) |
| Kasuga et al. [32]            | Total α-synuclein | Reesink et al. [48]           | Total α-synuclein | Syn1b (m)                   | Syn3b (m), Syn5d (m) |
| Tokuda et al. [44]            | Total α-synuclein | Oleogomeric α-synuclein       | 211 (m)         | Biotinylated 211 (m)        |                  |
| Aerts et al. [49]             | Total α-synuclein | Mollenhouer et al. [34]      | Total α-synuclein | 211 (m)                     |                  |
| Hong et al. [33]              | Total α-synuclein | Parnetti et al. [37]          | Total α-synuclein | 211 (m)                     |                  |
| Parnetti et al. [37]          | Total α-synuclein | Foulds et al. [50]           | Oligomeric α-synuclein | 211 (m)                   |                  |
| Wennstrom et al. [38]         | Total α-synuclein | Tateno et al. [36]            | Total α-synuclein | Not described               |                  |
| Park et al. [51]              | Total α-synuclein | Commercial kit (Invitrogen)   |                 |                             |                  |

m: monoclonal antibody; p: polyclonal antibody.

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\[ \text{toxic and could enhance pathological accumulation of} \]
\[ \text{α-synuclein and disease propagation [55]. Tokuda et al.} \]
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\[ \text{significantly higher in patients with PD than in patients with} \]
\[ \text{progressive supranuclear palsy (PSP) or AD [44]. In their} \]
\[ \text{study, the level of total α-synuclein in the CSF from PD} \]
\[ \text{patients tends to decrease [44]. Increased level of α-synuclein} \]
\[ \text{oligomers in CSF from PD patients was also shown by other} \]
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\[ \text{forms of α-synuclein detected in their studies using different} \]
\[ \text{methods may be heterogeneous in size and toxicity; hence,} \]
\[ \text{further validation is still needed.} \]


Table 3: Studies of quantification of α-synuclein level in blood of patients with DLB and other synucleinopathies.

| Methods                        | Samples*                | Results**                                                                 |
|--------------------------------|-------------------------|--------------------------------------------------------------------------|
| El-Agnaf et al. [57]           | ELISA Plasma            | α-Synuclein oligomers were elevated in patients with PD/DLB compared to controls. |
|                                | Cont (27), PD/DLB (34)  | The α-synuclein level was increased in patients with PD (79.9 pg/mL) and in those with MSA (78.1 pg/mL) compared with controls (76.1 pg/mL). The α-synuclein level was significantly higher in patients with PD than in those with MSA. |
| Lee et al. [58]                | ELISA Plasma            | The α-synuclein level was increased in patients with PD (79.9 pg/mL) and in those with MSA (78.1 pg/mL) compared with controls (76.1 pg/mL). The α-synuclein level was significantly higher in patients with PD than in those with MSA. |
|                                | Cont (51), PD (105), MSA (38) |                                |
| Duran et al. [59]              | ELISA Plasma            | The level of phosphorylated α-synuclein was higher in patients with PD than healthy controls. Antiparkinsonian treatment does not change plasma α-synuclein level. |
|                                | Cont (60), PD (95)      |                                |
| Foulds et al. [60]             | ELISA Plasma            | The α-synuclein level was elevated in patients with PD compared to healthy controls. |
|                                | (not described)         | The phosphorylated α-synuclein level in plasma quantified by ELISA as well as Western blot analysis is higher in patients with PD than in control subjects [60]. In their study, the level of α-synuclein remained stable within the same individuals at least over 3 months. |
|                                |                         |                            |
|                                |                         |                            |
| Shi et al. [61]                | Bead-based flowcytometric assay Plasma | No significant difference was found among patients with PD (36.8 ng/mL), AD (32.4 ng/mL), and those with healthy controls (39.5 ng/mL). |
|                                | Cont (95), AD (33), PD (117) | There was no difference in oligomeric and total α-synuclein in plasma between PD patients and controls. |
| Park et al. [51]               | ELISA Plasma            | The α-synuclein level was significantly lower in patients with PD than in those with age-matched healthy controls. Early-onset PD patients had lower α-synuclein levels than late-onset PD patients. |
|                                | Cont (29), PD (23)      | The α-synuclein level was significantly lower in patients with DLB (4.7 ng/mL) than in those with AD (7.0 ng/mL) and healthy controls (8.1 ng/mL). |
|                                |                         |                            |
| Li et al. [62]                 | IP-Western blot Plasma  | The α-synuclein level was significantly lower in patients with PD than in those with age-matched healthy controls. |
|                                | Cont (11), PD (27)      | Early-onset PD patients had lower α-synuclein levels than late-onset PD patients. |
| Laske et al. [63]              | ELISA Serum             | The α-synuclein level was significantly lower in patients with DLB (4.7 ng/mL) than in those with AD (7.0 ng/mL) and healthy controls (8.1 ng/mL). |
|                                | Cont (40), AD (80), DLB (40) |                                |

Arrows indicate increased (↑), comparable (→), and decreased (↓) levels of α-synuclein. * Sample numbers are shown in parenthesis. ** Values are indicated as mean or median. AD: Alzheimer's disease; Cont: controls; DLB: dementia with Lewy bodies; IP: immunoprecipitation; MSA: multiple system atrophy; PD: Parkinson's disease.

correlations, indicating that CSF total α-synuclein level may not be a sensitive biomarker of the preclinical phase of PD.

4. α-Synuclein in Blood

Several studies on the quantification of α-synuclein in blood have been carried out because drawing blood is much less invasive than lumbar puncture to obtain CSF from patients (Table 3). El-Agnaf et al. detected α-synuclein in plasma of patients with LBD by immunoprecipitation using an anti-α-synuclein antibody [27]. Subsequently, they found higher levels of α-synuclein oligomers in plasma from PD patients than in that from control subjects by ELISA [57]. A similar increase in α-synuclein level was observed in plasma from patients with PD and MSA [58, 59]. Lee et al. found that plasma α-synuclein level is higher in patients with PD than in those with MSA [58]. Duran et al. demonstrated that drugs such as L-dopa, dopamine agonists, and MAO/COMT inhibitors do not affect the plasma α-synuclein level in patients with PD [59]. The phosphorylated α-synuclein level in plasma quantified by ELISA as well as Western blot analysis is higher in patients with PD than in control subjects [60]. In their study, the level of α-synuclein remained stable within the same individuals at least over 3 months.

By contrast, Li et al. found a significantly decreased α-synuclein level in plasma from patients with PD by Western blot analysis, which detected only full-length monomeric α-synuclein [62]. Laske et al. also reported a similar decrease in serum α-synuclein level in DLB patients compared with AD patients and control subjects [63]. Comparable levels of plasma α-synuclein were found among patients with PD, AD, and control subjects in other studies [61].

5. Conclusions

Results of measurements of α-synuclein level in CSF and blood have been variable; hence, it is difficult to unequivocally conclude whether α-synuclein is a promising fluid biomarker of DLB and other α-synucleinopathies. More discriminating results for DLB patients could be obtained...
by examining specific α-synuclein species such as truncated, phosphorylated, and oligomeric species on the basis of their analogy to Aβ42 and phosphorylated tau species whose changes in levels are found to be reliable CSF biomarkers of AD. In addition, a multicenter study is required to validate the usefulness of α-synuclein as a biomarker by standardized methods of quantifying α-synuclein. Continuous efforts will be required to establish useful fluid biomarkers for early diagnosis of DLB and evaluation of disease-modifying therapeutics for DLB.

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