Serum NGAL is associated with distinct plasma amyloid-β peptides according to the clinical diagnosis of dementia in Down syndrome

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Serum NGAL is Associated with Distinct Plasma Amyloid-β Peptides According to the Clinical Diagnosis of Dementia in Down Syndrome

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Abstract

Background: The majority of people with Down syndrome (DS) develop dementia due to Alzheimer’s disease (AD). Neuropathological features are characterized by an accumulation of amyloid-β (Aβ) deposits and the presence of an activated immune response. Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a newly identified (neuro)inflammatory constituent in AD.

Objective: This study examines NGAL as an inflammatory marker in DS and its associations with plasma Aβ peptides according to the follow-up clinical diagnosis of dementia.

Methods: Baseline serum NGAL and plasma Aβ40, Aβ42, Aβ40/42, and Aβ42 were quantified in 204 people with DS. The diagnosis of dementia in DS was established by follow-up clinical assessments. The following study groups were characterized: DS with AD at baseline (n=67), DS without AD (n=53), and non-demented DS individuals that converted to AD (n=84).

Serum NGAL was analyzed in 55 elderly non-DS, non-demented people.

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INTRODUCTION

The prevalence of Down syndrome (DS), or trisomy 21, in the adult population is estimated to be approximately 1 in 700–1200 live births [1, 2] and is the most common genetic incidence of intellectual disability in humans [3]. A vast majority of people with DS develop Alzheimer’s disease (AD) pathology, which is mainly characterized by amyloid-β (Aβ) deposition in the brain [4]. A high prevalence of the clinical diagnosis of dementia (50–70%) in DS is respectively found in mid- to late life [5, 6]. This phenomenon is due to a triplication of the human chromosome 21 (HSA21) that harbors several genes, i.e., amyloid-β protein precursor (AβPP) and β-site APP cleaving enzyme 2, that are responsible for the increased production of Aβ [4]. In addition to increased brain Aβ levels, individuals with DS have increased plasma Aβ levels compared to people without DS [7–9].

Inflammatory-associated genes on HSA21 are likely overexpressed in DS and have been suggested to contribute to an aberrant immune regulation that is characterized by a pro-inflammatory environment [10, 11]. Increased pro-inflammatory cytokines have been identified in brain tissue of people with DS [12] as well as in their circulation [13, 14], which might even be present during their early adolescence [15]. Furthermore, increased neuroinflammatory processes have been suggested to play an important role in the pathophysiological processes of DS and AD [10, 11]. This study focuses on Neutrophil Gelatinase-Associated Lipocalin (NGAL), a newly introduced inflammatory constituent in the pathophysiology of AD [16]. NGAL is a 25 kDa acute phase protein that is also known as Lipocalin-2, Siderocalin, 24p3, or Unerocalin [17]. Human studies showed that increased blood NGAL levels are associated with risk factors for AD, mild cognitive impairment [18], late-life depression [19], and elderly depressed females with impaired recall memory [20]. Serum NGAL is also increased in adult and elderly DS people compared to adult people without DS [21]. Primary neuronal cell cultures studies showed that NGAL mRNA and protein production is increased by Aβ42 [22] and Aβ40 [23]. Furthermore, NGAL impairs neuroprotective mechanisms in neurons and exacerbates Aβ42-mediated neuronal cell death [16, 22]. These studies in essence indicate that NGAL is an important inflammatory marker that is involved in the pathophysiology of AD.

The aims of this study were: 1) to validate if NGAL levels are elevated in DS individuals compared to non-DS controls; 2) to determine whether baseline serum NGAL levels are associated with the clinical diagnosis of dementia in DS, i.e., DS subjects with established AD at baseline (demented), without AD (non-demented), and non-demented DS people that converted to dementia over time; and 3) to associate serum NGAL with plasma Aβ42, Aβ40, Aβ42/Aβ40, Aβ42, Aβ40, or Aβ42/Aβ40 in these groups.

MATERIALS AND METHODS

Study population

In total, 204 people with DS were included in this study. All participants were enrolled between 1 December 1999 and 1 December 2003 at an age of 45 years or older and are part of the previously published Rotterdam DS cohort [24–27]. Fasting venous blood samples were obtained in the morning, once at baseline of the study. Blood was directly processed and plasma and serum were stored at −80°C and −20°C, respectively. Ethical approval for this study was granted by the ethical review board of Erasmus MC Rotterdam (METC protocol number: MEC 185.974/1999/202). Written informed consent to participate and to provide blood samples was obtained from legal representatives (relatives and/or caretakers), after written information was provided. Written consent was also obtained from persons with DS who had the mental capacity to consent. To determine whether NGAL levels are increased in DS compared to healthy people.
non-DS persons, serum samples from 55 healthy non-
DS persons were obtained from the Antwerp Biobank
of the Institute Born-Bunge. These volunteers did not
have any illness, clinical variables nor did they use
any medication which may have interfered with NGAL
levels. Ethics approval for human sample collection of
serum was granted by the Medical Ethical Committee
of the Middelheim General Hospital (Antwerp, Bel-
gium) (Approval numbers 2805 and 2806). The study
was also conducted in compliance with the Helsinki
Declaration.

Clinical AD assessment

As previously described [24, 28], AD was assessed
at baseline using the International Classification of
Diseases (ICD)-10 from the World Health Organization
[29], according to the guidelines of the Special Interest
Research Group on Aging of the International Associa-
tion for the Scientific Study of Intellectual Disabilities
(IASSID) to diagnose dementia in adults with intellec-
tual disabilities [29–31]. These criteria emphasize on
non-cognitive symptoms, which are often prominent
signs of dementia in adults with intellectual disabili-
ties. Importantly, ICD-10 criteria have been modified
for use in adults with intellectual disabilities. It has
been shown that the AD criteria of the ICD-10 and
the Diagnostic and Statistical Manual of Mental Disor-
ders (Fourth Edition) diagnosed dementia in the same
adults with DS [32] and that these diagnostic criteria
show ‘substantial reliability and satisfactory validity
in other intellectual disabilities as well [33].

In our study, study participants were systematically
screened for dementia and examined in person by a
clinician. The demented individuals met the ICD-10
criteria at intake and had an insidious and progressive
course of the disease. In addition, validated functional
questionnaires such as the Dementia Questionnaire for
persons with an intellectual disability (DMR) [34], Social
Competence Rating Scale for persons with
an intellectual disability (SRZ) [35], and, Vineland
adaptive behavior scales [36] were retrospectively com-
pleted by family or caretakers every twelve months
(continues until present if the person is still alive).

Three diagnostic groups were defined based on the
AD assessment (ICD-10) and annual follow-up (DMR,
SRZ, and Vineland): demented at baseline (n = 67),
converted (n = 84), and non-demented (n = 53) DS sub-
jects. DS people that converted to AD, was clinically
established before January 2007, thus within 3 to 7
follow-up years after intake and blood sampling. All of
the DS participants in this study were assessed annually
from baseline until January 2013 and were therefore
followed for 10–14 years since baseline of this study.

Body mass index (BMI) at baseline was computed
as weight in kilograms divided by height in square
meters.

Analyses of blood samples

Blinded analysis of serum NGAL [16], plasma
Aβ40, Aβ42, and truncated Aβ40, and Aβ42 [26] and
apolipoprotein E (ApoE) genotype [25] was performed
as previously described.

Blood (20 ml) obtained via the antecubital vein was
collected in tubes containing K3-EDTA and immedi-
ately processed for platelet preparation. Platelet-rich
plasma and blood cells fractions were separated by
centrifugation. Platelet-rich plasma was removed and
centrifuged again to obtain platelet pellets. Platelets
were suspended in sucrose containing 5% dimethyl-
sulfoxide to maintain membrane integrity and stored
at –80 oC until use.

Covariates

Age, gender, and BMI were included as covariates
based on previous findings [19]. The presence of the
ApoE ε4 allele was included as covariate as well since
it can affect serum inflammatory markers [37] and
possibly plasma Aβ levels [38]. Furthermore, blood
platelets were included as final confounding factor,
since previous studies described them as an important
source of plasma Aβ40 and Aβ42 [39, 40]. Recently, in
a large cohort with elderly participants we showed that
increased NGAL levels were associated with the use of
anti-inflammatory medication [19]. Therefore, the use
of non-steroidal anti-inflammatory drugs (NSAIDs)
was included as final covariate. Only three DS peo-
ple used corticosteroids and they were therefore not
included as covariate.

Statistical analyses

In order to obtain a normal distribution of the serum
NGAL levels, four identified outliers were trimmed to
304.19 ng/ml resulting in a skewness of 0.65 and
kurtosis of −0.25. As some covariates had missing
data, we imputed the mean value of the other subjects
in case of continuous variables or the most frequent
score in case of dichotomous or nominal data. Variables
with missing values in the whole sample were: BMI
(n = 5), ApoE (n = 4), platelets (n = 9), Aβ42 (n = 11),
Aβ42/ Aβ40 (n = 10), Aβ42/ Aβ40 (n = 11), Aβ42/ Aβ40 (n = 11),


RESULTS

Population demographics

Demographics and clinical information of non-DS controls and DS persons are shown in Table 1. Non-DS controls were older than DS people and DS subjects with dementia at baseline and people whom converted to dementia during follow-up were older than the non-demented DS group. No significant differences were observed for gender, BMI, ApoE e4 allele, or platelet numbers between groups. Significant differences in NGAL levels were found between the non-DS people and the DS groups. While the presence of ApoE e4 allele has been associated with increased blood pro-inflammatory cytokines in humans [37, 42], results from this study show that NGAL levels were not significantly associated with the presence of the ApoE e4 allele (unpaired t-test, t(198) = 0.416, p = 0.678).

Serum NGAL levels in healthy non-DS volunteers compared to DS individuals

Differences in NGAL levels between the studied groups was further explored, since significant differences in NGAL levels between non-DS controls, demented, converted and non-demented DS groups (ANOVA, F = 10.12, df = 3, p < 0.001) were found. NGAL levels were significantly lower in non-DS controls, demented, converted and non-demented DS groups (ANOVA, F = 10.12, df = 3, p < 0.001) subjects (Fig. 1). Moreover, analysis with ANCOVA (F(3, 253) = 8.69, p < 0.001) and Bonferroni post hoc tests showed that serum NGAL levels were increased in demented

Table 1

Demographics and clinical info of study participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-DS controls</th>
<th>Demented DS</th>
<th>Converted DS</th>
<th>Non-demented DS</th>
<th>Statistics for DS participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female</td>
<td>52 (66)</td>
<td>26 (39)</td>
<td>33 (39)</td>
<td>21 (40)</td>
<td>χ² = 0.21, df = 2, p = 0.91</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>75.5 (9.4)²</td>
<td>54.5 (5.9)²</td>
<td>51.3 (5.3)²</td>
<td>49.7 (4.3)</td>
<td>F(3, 251) = 40.38, p &lt; 0.001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25 (4.8)</td>
<td>25.7 (3.9)</td>
<td>25.4 (3.8)</td>
<td>F(2, 198) = 0.41, p = 0.67</td>
<td></td>
</tr>
<tr>
<td>ApoE e4 allele, n (%)</td>
<td>22 (33.8)</td>
<td>21 (32.6)</td>
<td>14 (26.4)</td>
<td>χ² = 1.36, df = 2, p = 0.51</td>
<td></td>
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<tr>
<td>Platelets, mean (SD)</td>
<td>232.1 (78.4)</td>
<td>224.7 (90.9)</td>
<td>232.1 (73.6)</td>
<td>F(2, 192) = 0.19, p = 0.83</td>
<td></td>
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<tr>
<td>NSAID, n (%)</td>
<td>11 (19)</td>
<td>10 (12.8)</td>
<td>3 (6.3)</td>
<td>χ² = 4.40, df = 2, p = 0.16</td>
<td></td>
</tr>
<tr>
<td>NGAL, mean (SD)</td>
<td>114.4 (52.2)</td>
<td>162.2 (37.5)</td>
<td>155.2 (53.6)</td>
<td>163.8 (63.7)</td>
<td>F(3, 253) = 10.12, p &lt; 0.001</td>
</tr>
</tbody>
</table>

²Non-DS controls versus demented at baseline, converted and non-demented p < 0.001. χ², x-square; n, number; y, years; SD, standard deviation; BMI, body mass index; ApoE, Apolipoprotein E; NSAID, non-steroidal anti-inflammatory drugs; NGAL, neutrophil gelatinase-associated lipocalin; AD, Alzheimer’s disease; DS, Down syndrome.
by dementia diagnosis. As shown in Table 2, higher serum NGAL levels were significantly associated with higher plasma \(A\beta_{40}\) levels in the non-demented DS group, which remained significant after adjustments for confounding factors: age, gender, BMI, ApoE e4, and platelets, but the significant association was lost after including NSAIDs as confounding factor.

Linear regression analyses showed a significant association of higher NGAL levels with higher \(A\beta_{42}\) levels. However, significance was lost after correcting for confounding factors. Higher NGAL levels were significantly associated with a lower \(A\beta_{42}/A\beta_{40}\) ratio in converted DS people. This association lost significance after adjusting for age, gender, BMI, ApoE e4, and platelets, however remained significant after including NSAIDs as covariate. Higher NGAL showed a strong association with higher \(A\beta_{40}\) levels in non-demented DS people independent of confounding factors. A significant association of higher NGAL levels with higher \(A\beta_{42}\) levels was found in the demented DS group, which remained significant after correcting for age, gender, BMI, ApoE e4, and platelets. Inclusion of NSAIDs as covariates consequently resulted in a significant association of increased NGAL levels with increased \(A\beta_{42}\) levels in the demented and non-demented DS individuals and decreased \(A\beta_{42}\) levels in the converted DS people. Increased NGAL levels were significantly associated with a decreased \(A\beta_{42}/A\beta_{40}\) ratio in converted DS subjects. This association remained marginally significant (\(p = 0.055\)) after correcting for age, gender, BMI, and ApoE e4. Accordingly, the association remained significant after inclusion of platelet levels and NSAIDs.

**DISCUSSION**

The current study shows that serum NGAL levels were increased in elderly DS subjects compared to healthy, non-DS controls. Furthermore, serum NGAL levels were not associated with the clinical symptoms of dementia in DS. However, definite associations of NGAL levels with \(A\beta_{40}, A\beta_{42}\), their truncated species, and their ratios depended on the follow-up clinical diagnosis of dementia. Therefore, these results support the notion that a pro-inflammatory environment is present in DS and that NGAL is an inflammatory marker that is significantly associated with distinct species of \(A\beta\), moderated by the presence or absence of the clinically established dementia diagnosis over time.
Table 2
Association of serum NGAL levels with plasma amyloid-β species, including covariates, per diagnostic DS group

<table>
<thead>
<tr>
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<th>Model 1</th>
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<td></td>
<td>Demented</td>
<td>Converted</td>
<td>Non-demented</td>
<td>Demented</td>
<td>Converted</td>
<td>Non-demented</td>
<td>Demented</td>
<td>Converted</td>
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<td>Unadjusted</td>
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<td>Adjusted</td>
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<tr>
<td></td>
<td>B(SE)</td>
<td>p</td>
<td>B(SE)</td>
<td>p</td>
<td>B(SE)</td>
<td>p</td>
<td>B(SE)</td>
<td>p</td>
</tr>
<tr>
<td>ALβ0</td>
<td>0.45 (0.23)</td>
<td>0.24</td>
<td>0.064</td>
<td>3.25 (1.36)</td>
<td>0.39</td>
<td>0.02</td>
<td>192.35 (155.82)</td>
<td>0.024</td>
</tr>
<tr>
<td>ALβ24</td>
<td>0.30 (0.16)</td>
<td>0.21</td>
<td>0.056</td>
<td>-1.09 (1.23)</td>
<td>-0.10</td>
<td>0.96</td>
<td>-110.10 (43.19)</td>
<td>-0.13</td>
</tr>
<tr>
<td>ALβ24/ALβ0</td>
<td>4.46 (2.21)</td>
<td>0.28</td>
<td>0.042</td>
<td>2.75 (1.66)</td>
<td>0.23</td>
<td>0.10</td>
<td>2.03 (0.29)</td>
<td>0.46</td>
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<tr>
<td>Model 2</td>
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</table>
|                | Model 1   | Adjusted for age, gender, BMI, and ApoE ε4 allele. Model 2: Model 1, added with platelet levels. Model 3: Model 1 and 2, added with use of NSAID. NGAL, neutrophil gelatinase-associated lipocalin; Aβ, amyloid-β; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drugs; DS, Down syndrome.
Serum NGAL levels in DS and healthy non-DS subjects: The role of Aβ

As mentioned above, our results show that serum NGAL levels in older DS people were significantly increased compared to healthy elderly non-DS people. This finding is in accordance with a study by Dogliotti and colleagues showing that serum NGAL levels are significantly increased in adults and elderly people with DS compared to adult non-DS healthy controls [21]. Because NGAL is encoded on human chromosome 9 [43], increased NGAL levels may not be directly attributed to the triplication of HSA21.

Importantly, studies with neuronal cell cultures have shown that NGAL protein and mRNA production is stimulated by Aβ42 [22] and Aβ40 [23]. In this regard, a robust increase of NGAL protein levels is present in postmortem brain tissue of AD patients with a similar regional distribution pattern as the Aβ pathology [16]. These studies, therefore, indicate that increased NGAL production may be the result of Aβ accumulation that is characteristically present in DS brain, already at a young age. NGAL thus may be related to Aβ-related pathophysiological processes in the development of dementia in DS. Correspondingly, the association of serum NGAL with different plasma Aβ species was further investigated in this study population.

Associations between serum NGAL levels and different plasma Aβ species

Increased serum NGAL levels were: 1) positively associated with Aβ42 and Aβ40 in the demented DS group; 2) positively associated with Aβ42 and Aβ40 in non-demented DS subjects; and 3) negatively associated with Aβ42/Aβ40 and Aβ42/Aβ40 ratios in those non-demented DS individuals that converted to dementia over time. These findings are of interest considering the neuropathological regulation of Aβ accumulation in DS during lifetime. Neuropathological studies in DS demonstrated that sequential changes of Aβ plaque formation occur during the lifespan in people with DS, which can provide insights concerning the associations of NGAL with Aβ found in this study. Intraneural Aβ42, but not Aβ40, has been reported in very young DS people (3 years old) [44]. With increasing age, extracellular Aβ42 plaques gradually accumulate and mature [44, 45]. Extracellular deposition of Aβ42 in senile plaques precedes the presence of Aβ40 by approximately a decade [45, 46]. During the later stages in life (around 50 years), Aβ40 accumulation gradually increases in mature plaques and, moreover, it is the predominant Aβ species in cerebral amyloid angiopathy in DS [45, 47]. Although almost all individuals with DS have Aβ deposition resembling AD neuropathology [48, 49], there is a wide variation in the age at onset of dementia. This is due to complex mechanisms that are involved in Aβ regulation during the progression to dementia [50]. In this respect, alterations in the ratio between Aβ42 and Aβ40 may function as a significant predictor for the development of dementia due to AD [51, 52].

The positive association of increased NGAL with Aβ40 in non-demented DS subjects may indicate that Aβ40 has not yet accumulated into plaques in the brain resulting in a negative correlation with NGAL in the peripheral blood circulation. This association remained significant after adjustments for confounding factors were made. On the other hand, the association of increased NGAL with Aβ42 in the demented DS group may be explained by microglial processes during later stages of Aβ pathology in DS. It was shown that activated microglia and astrocytes were present in diffuse and neuritic plaques [53] and microglia cells can clear Aβ42 from the brain to compensate for Aβ pathology [54]. Alternatively, increased inflammatory processes associated with microglia activation may induce an increase in AβPP and consequently an increase in Aβ42 production [10]. Both of these above-mentioned processes can lead to increased levels of circulating Aβ42 peptides. However, this significant association diminished after adjustments for age, gender, BMI, and ApoE e4 allele. Interestingly, increased NGAL levels were negatively associated with the Aβ42/Aβ40 ratio in the converted DS group. This association remained marginally significant after the adjustments for age, gender, BMI, and ApoE e4 were made. Considering changes of Aβ40 and Aβ42 in the brain described in the abovementioned neuropathological studies and the association of increased serum NGAL with plasma Aβ40 in non-demented and Aβ42 in demented DS subjects, it is reasonable to speculate that NGAL is associated with a shift in Aβ regulation present in people with DS whom are in process of converting to dementia. Moreover, it has been previously shown that truncated Aβ increases in parallel to their full length peptides in DS brain [55]. Similar associations of NGAL with full length Aβ and their truncated isoforms can therefore be expected. Indeed, our findings persisted for Aβ30-40 and Aβ42-43, similarly to their full-length isoforms. Generally, the association of NGAL levels was even stronger with truncated forms of Aβ than with full length Aβ.
The association of NGAL levels with Aβ42/Aβ40 and Aβ40/Aβ42 ratio strengthened after adjusting for NSAIDs as confounding factor. In addition, the associations of NGAL levels with Aβ42 levels became significant in all of the DS groups. In a previous cohort with a large population of elderly participants, we found that increased NGAL levels were associated with the use of anti-inflammatory medication, which may be explained by underlying somatic conditions [19]. Therefore, the increase in significance of associations after correcting for NSAIDs may be due to correcting for underlying physical ailments related to inflammatory conditions, explaining additional variance in NGAL levels unrelated to levels of Aβ peptides.

The relationship between NGAL, neurodegeneration, and DS

Fundamental research indicates that NGAL plays a role in several mechanisms involved in the pathophysiology of AD. Cell culture studies have shown that NGAL induces pro-apoptotic signaling cascades in neurons and exacerbates oligomeric Aβ42-mediated neuronal cell death [16, 22]. In addition, NGAL can aggravate oxidative damage to neuronal cells [22, 56]. This is of importance since people with DS have an increased susceptibility for oxidative stress due to an extra copy of superoxide dismutase 1 [5]. Furthermore, NGAL exerts neuro-immunomodulatory effects. Increased NGAL induces astrocytes and microglia to a pro-inflammatory phenotype and suffices their anti-inflammatory functioning [57, 58], whereas elimination of NGAL reduced neuroinflammation and neuronal damage after neuronal injury in mice [59, 60]. As basal NGAL levels increase with age in DS [21], it could increase the sensitivity toward toxic forms of Aβ and oxidative stress and, therefore, contribute to neurodegeneration and, consequently, the development of clinical symptoms of dementia that occur mid- to late life in DS.

Plasma Aβ as a potential biomarker for dementia conversion in DS

Blood-based biomarkers that can predict the conversion to dementia in DS are much desired because they would provide a valuable tool to enable and plan optimal adaptive caregiving. In addition, biomarkers can improve our knowledge of aberrant physiological processes involved during the disease progression. Several studies have investigated the association of plasma Aβ in DS and their potential as diagnostic markers for dementia with inconsistent results [61]. A possible explanation for these discrepancies is that changes of plasma Aβ concentrations in relation to the status of dementia might not be large enough for its use as a biomarker. In this respect, results from this study indicate that the association of NGAL with Aβ species may provide an indication of changes in Aβ accumulation during the progression to dementia in DS.

Strengths and limitations

This study has several strengths worth mentioning. This study consisted of a large DS population group. In addition, AD diagnosis at baseline using the ICD-10 criteria, follow-up clinical assessment in this DS population using validated questionnaires for dementia in DS enabled the identification of those DS individuals that remained non-demented or converted to dementia over time. Several important confounding factors were included that were shown to have potential associations with NGAL and Aβ. The role of circadian influences on blood markers was minimized by obtaining fasting morning blood samples. In addition, NGAL possesses great storage stability, i.e., NGAL can be subjected to several freeze-thaw cycles without affecting outcomes of its analyses which make it suitable for application as a biomarker [62].

In order to properly interpret the results presented in this study, study limitations ought to be acknowledged. ANCOVA analysis did not show a significant interaction of Aβ40 and Aβ42/Aβ40 with the diagnosis of dementia, with NGAL as dependent variable and therefore, outcomes from these findings should be interpreted with caution. Increased significant associations of NGAL levels with Aβ40/Aβ42 and Aβ40/Aβ42 ratio and Aβ42 after correcting for NSAIDs may be due to underlying ailments that were not documented in this study. Results of this study are based on baseline blood sampling, but longitudinal studies with clinical assessments of dementia in DS accompanied with follow-up blood collection is warranted. Of particular interest would be to follow DS people from a younger age (<40 years) to accurately evaluate the association of NGAL with Aβ in the progression to dementia.

CONCLUSIONS

In conclusion, this study confirmed that serum NGAL levels are increased in elderly DS subjects compared to elderly non-DS controls and strengthens the notion that an increased pro-inflammatory condition...
is present in people with DS. Furthermore, NGAL was not associated with either diagnosed dementia or progression to dementia in DS. However, serum NGAL levels were associated with different plasma Aβ species according to the clinical symptoms of dementia. Therefore, the association of serum NGAL with plasma Aβ may reflect the neuropathological regulation of Aβ accumulation and circulation in accordance with the clinical symptoms of dementia in DS. Finally, the measurement of circulating NGAL levels may improve the sensitivity of plasma Aβ as a biological marker for dementia in DS that merits further investigation.

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Authors’ disclosures available online (http://j-alz.com/manuscript-disclosures/14-2514r1).

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