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# Feasibility of Lumbar Puncture in the Study of Cerebrospinal Fluid Biomarkers for Alzheimer's Disease in Subjects with Down Syndrome

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**Abstract**.
**Background:** Alzheimer's disease (AD) is the main medical problem in older adults with Down syndrome (DS). Studies of cerebrospinal fluid (CSF) AD biomarkers are limited and the feasibility of lumbar puncture (LP) is controversial in this population.
**Objective:** To analyze the frequency of complications after a LP in DS.
**Methods:** We collected data from 80 adults with DS that underwent a LP within the Down Alzheimer Barcelona Neuroimaging Initiative. Demographics, cognitive status, headache history, and presence of complications after the LP were recorded in every subject. In 53 of them (*active* group), this information was collected following a semi-structured and validated protocol that actively looks for complications. Other variables related to the LP procedure were also recorded. A telephone interview to the caregiver was performed 5–7 days after the procedure to ask about complications. Data from 27 subjects (*clinical practice* group), from whom the presence of complications was obtained in a medical follow-up visit within the three months after the LP, were also included.
**Results:** There were no adverse events in 90% of our participants. The most frequent complication was headache (6.25%); only one subject reported a typical post-lumbar puncture headache with moderate severity that required analgesic treatment. Dizziness (3.75%) and back pain (1.25%) were also reported. All the participants that reported complications belonged to the *active* group.

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**Conclusion:** LP can be safely performed to study CSF biomarkers in DS. The reported complications are qualitatively similar to the general population, but are less frequently reported, even when actively searched for.

Keywords: Alzheimer's disease, biomarkers, cerebrospinal fluid, Down syndrome, complications, lumbar puncture

## INTRODUCTION

Down syndrome (DS) is the most frequent genetically determined form of intellectual disability [1]. Its pathogenesis relies on the trisomy of chromosome 21 which associates multiple comorbidities [2, 3]. Following the advances in medical and general care sciences, life expectancy of individuals with DS has dramatically increased [4–6] and, in consequence, the incidence of age-associated comorbidities has also augmented [7].

The International Working Group-2 criteria for the preclinical states of Alzheimer's disease (AD) consider DS as a genetically determined form of AD [8]. Thus, AD comprises the most important medical problem in adults with DS [1]. The pathophysiological mechanism of AD in DS seems to rely on the overexpression of some genes involved in the amyloidogenic pathway that are also encoded by chromosome 21, such as amyloid precursor protein [9, 10]. Epidemiological studies have found a prevalence of dementia of 55% between 40–49 years [11], 77% between 60–69 years, and 100% in people aged more than 70 years [12]. However, despite this exponential increase in dementia prevalence after age forty, the onset of AD is highly variable and may depend upon genetic and environmental factors [13]. The diagnosis of dementia in DS is more difficult than in the general population due to the intellectual disability associated to the syndrome and because the clinical presentation might differ from that in the general population. Clinical symptomatology can present as a decline in memory as in the general population, but frequently starts with changes in personality and behavior disturbances or it can start with declines in other cognitive domains such as dysexecutive symptomatology [1, 10, 11]. These atypical presentations, together with the frequent medical and psychiatric comorbidities, may complicate the differential diagnosis of AD in DS.

Biomarkers, therefore, might prove especially useful in this population. Cerebrospinal fluid (CSF) biomarkers such as amyloid-β1-42, tau, and phosphorylated tau allow the tracking of neuropathological features of AD [14–16]. The study of CSF biomarkers, especially in those atypical presentations, could help to achieve an earlier diagnosis of AD and a more appropriate management of the patient.

The feasibility of lumbar puncture (LP) to analyze CSF biomarkers in sporadic AD has been already addressed [17, 18] and proven safe in the general population. Post-lumbar pressure headache (PLPH) is the most frequent complication, affecting up to 25% patients that undergo a LP. However, only less than 5% patients report a significant complication, such as severe headache, or need medical treatment. Other mild complications include back pain, dizziness, and nausea [17, 18].

The performance of a LP in DS for AD diagnosis remains controversial and the safety of LP has not been studied in this population. Our primary aim was to determine the frequency of complications of LP to study CSF AD biomarkers in DS. Our secondary objective was to perform an exploratory analysis on the factors that were associated with complications.

## METHODS

All subjects were recruited at the Barcelona Down Medical Center (BDMC) in Barcelona between February 2013 and July 2016. The BDMC is a non-profit organization that assists about 2,000 subjects with DS living in Catalonia. In 2014, together with the Memory Unit of Sant Pau Hospital, a health plan to screen for AD dementia in adults with DS was launched. This health plan includes yearly clinical, neurological, and neuropsychological assessments. The neuropsychological evaluation uses the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities battery (CAMDEX-DS), which is a validated tool to assess cognitive impairment (CI) in subjects with DS [19–21]. Based on the neurological visit and the neuropsychological assessment, subjects were classified in four groups based on their cognitive status: DS-without CI (DS-wCI), when there is no evidence of impairment of cognitive functions; DS-non-neurodegenerative etiology (DS-ndeg), when there is a cognitive impairment most probably due to a medical or psychiatric comorbidity;

DS-prodromal AD (DS-pAD), when there is an evidence of cognitive impairment which does not meet criteria for dementia; and DS-AD when there is a full blown AD dementia. In the setting of this health plan, subjects are invited to participate in a clinical research project named DABNI (Down syndrome Alzheimer Neuroimaging Initiative Program). This initiative consists of a multimodal AD biomarkers study in DS with the aim of understanding the AD natural history in DS. These biomarker studies include a LP for CSF analysis.

The study has been carried out in strict accordance with international ethical guidelines for medical research in humans. This protocol was reviewed and initially approved by the local independent Ethics Committee and reported to the Minister of Justice according to the Spanish law for research in people with intellectual disabilities in September 2012. It was performed according to the stipulations made in the updated Declaration of Helsinki. All participants were included after obtaining the written informed consent approved by the ethics committee from both the legal representative and the subject when the participant was able to consent. Before including any subject in the study, the investigator informed the participant and their legal tutor of the objectives, methods, and potential risks of the study or any inconvenience this may cause. The level of protection of confidentiality concerning personal data was ensured as required by the Spanish law (LOPD 15/1999).

We prospectively collected data from those participants who underwent a LP. In every case, a neurologist with expertise in the procedure carried out the LP. The procedure was performed either in sitting or lying position, using the pen-point "atraumatic" needle (Whitacre-22G) or the cutting-edge Quincke needle (20G or 22G), introducing the bevel parallel to dural fibers. Patient positioning and needle characteristics were decided based on the neurologist's preference according to each patient's characteristics. CSF was collected by free-flow/dripping. All participants received similar recommendations after the procedure: they were advised to rest 24 hours after the LP and to increase fluid intake.

According to the method of recording the presence of complications, participants were divided in two groups (Fig. 1):

–*Active* group: An active search for complications was performed; data were systematically collected following the protocol of a larger international initiative led by the Alzheimer's Association and the University of Gothenburg [17, 18]. Five to seven days after the LP, caregivers were contacted to answer a semi-structured telephone interview about complications. The protocol also registered variables related to the moment of the LP: position, needle characteristics, patient positioning, needle type, volume of CSF extracted, attempts needed for CSF removal, visually hematic CSF staining, and resting time after CSF acquisition.

–*Clinical practice* group: The information of the presence of complications was obtained in a medical follow-up visit performed within the next three months after the LP. Data related to the moment of the LP were not systematically recorded.

In both groups, demographic information, intellectual disability grade (DSM-5 criteria), cognitive status, previous history of headache, and the presence of complications were registered in every subject. The outcome variables that were systematically obtained included headache, local back pain, dizzi-

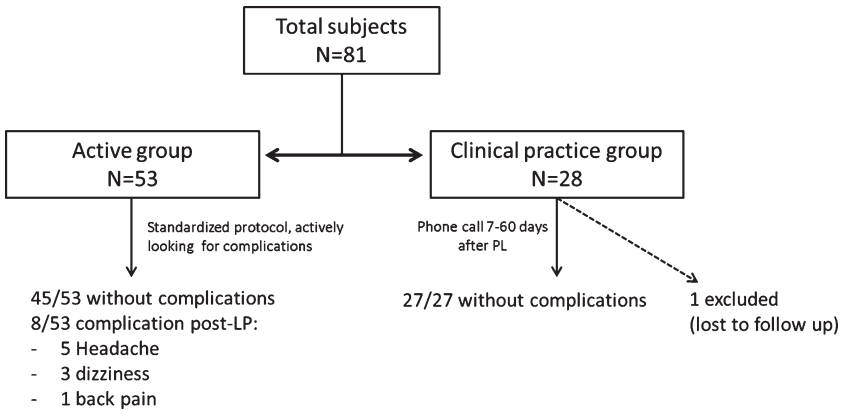


Fig. 1. Flow-chart of participants and reported complications.

ness, and nausea, but other possible complications could be registered if present. Regarding headache; we recorded intensity of the pain, defined as mild (no treatment or mild analgesics), moderate (patient had to stay in bed for periods of the day), or severe (invalidating or requiring hospitalization); headache duration (<2 days, 2–4 days, >4 days); and headache classification as fulfilling the International Headache Society criteria of PLPH [18] or as non-specific.

We started to perform LPs in patients with DS before the implementation of the referred protocol. This group reflects better the usual clinical (and research) practice, since participants do not usually undergo a structured protocol and calls to actively look for complications. Therefore the later group allowed us to perform a comparison with the usual clinical practice.

Statistical analyses were performed with the software Statistical Package for the Social Sciences v.23.0 (http://www-01.ibm.com/software/es/analytics/spss/). We analyzed the differences in the frequency of complications using Chi-Square tests for categorical and t-student tests for continuous variables. Variables with $p$-values <0.20 in the bivariate analysis and/or with clinical interest were included in logistic multivariate regression model. Variables with $p$-values <0.05 were considered statistically significant.

## RESULTS

Data from 81 consecutive participants were collected for this study: 53 from the *active* group and 28 from the *clinical practice* group. One subject in the *clinical practice* group was excluded due to the impossibility of being contacted after the LP (Fig. 1).

Demographics are summarized in Table 1. Subjects in the *active* group were younger than those in the *clinical practice* group ($p = 0.016$).

There were no reported complications in 90% of the participants in the overall sample. Headache was the most frequent complication, affecting 5 (6.3%) participants. Dizziness was present in 3 subjects (3.75%) and 1 in of them (1.3%) back pain was also referred. No other complications were reported. All the participants that presented any complication belonged to the *active* group, whose procedural characteristics and type of complications are shown in Table 2. The frequency of complications was, thus, higher in the *active* than in the *clinical practice* group ($p = 0.046$).

With respect to headache, a typical PLPH with moderate severity occurred in 1 subject (1.3%). The remaining 4 (5%) had a mild unspecific headache. In the patient diagnosed with PLPH, the pain started in the first 24 hours after the procedure, required treatment with acetylsalicylic acid, and remitted between 2 and 4 days later. Among the 4 patients with an unspecific headache, the pain started in the first 24 hours in 3 subjects and 24 hours after the procedure in one. The duration of the pain was less than 24 hours in three patients—one of them was recommended to drink a caffeinated beverage—and between 1 and 2 days in one. A previous history of a mild sporadic headache was present in 2 subjects (20% of those who presented headache after LP).

Table 1
Demographics of the participants

| Variable | | *Active* group ($n = 53$) | *Clinical practice* group ($n = 27$) | $p$ value |
|---|---|---|---|---|
| Age, mean (SD) | | 41.85 (11.95) | 44.63 (8.63) | 0.016 |
| Gender, $n$ (%) | Male | 29 (54.7%) | 18 (66.7%) | 0.305 |
| | Female | 24 (45.3%) | 9 (33.3%) | |
| Weight, mean (SD)* | | 62.90 (10.67) | 64.94 (10.1) | 0.470 |
| Intellectual disability, $n$(%) | Mild | 10 (18.9%) | 4 (14.8%) | 0.800 |
| | Moderate | 29 (54.7%) | 18 (66.7%) | |
| | Severe | 11 (20.7%) | 3 (11.1%) | |
| | Profound | 3 (5.7%) | 2 (7.4%) | |
| Diagnosis, $n$ (%) | DS-wCI | 28 (52.8%) | 15 (55.6%) | 0.725 |
| | DS-ndeg | 3 (5.7%) | 3 (11.1%) | |
| | DS-pAD | 9 (17%) | 3 (11.1%) | |
| | DS-AD | 13 (24.5%) | 6 (22.2%) | |
| Complications, $n$ (%) | No | 45 (84.9%) | 27 (100%) | 0.046 |
| | Yes | 8 (15.1%) | 0 (0%) | |

AD, Alzheimer's disease; DS, Down Syndrome; ndegCI: non-neurodegenerative cognitive impairment; pAD, Prodromal Alzheimer's disease; wCI, without cognitive impairment. *Weight data were obtained from 46 patients of the *active* group and 24 subjects of the *clinical practice* group.

Table 2
Procedure characteristics and complications recorded in the active group ($n = 53$)

| Variable | | |
|---|---|---|
| Headache history, *n* (%) | No/rarely | 51 (96.2%) |
| | Mild/now and then | 2 (3.8%) |
| | Yes/chronic or relapsing | 0 (0.0%) |
| Needle type, *n* (%) | Q-20 | 2 (3.8%) |
| | Q-22 | 16 (30.2%) |
| | W-20 | 1 (1.9%) |
| | W-22 | 34 (64.1%) |
| Position, *n* (%) | Lateral decubitus | 9 (17.0%) |
| | Sitting | 44 (83.0%) |
| Volume, mL (mean-SD) | | 12.04 (4.19) |
| Complications, n (%) | No | 45 (84.9%) |
| | Yes | 8 (15.1%) |
| Headache, *n* (%) | No headache | 48 (90.6%) |
| | Mild | 4 (7.5%) |
| | Moderate | 1 (1.9%) |
| | Severe | 0 (0.0%) |
| Headache type, *n* (%) | No headache | 48 (90.6%) |
| | Typical PLPH | 1 (1.9%) |
| | Unspecific | 4 (7.5%) |
| Back pain, *n* (%) | No | 52 (98.1%) |
| | Yes | 1 (1.9%) |
| Dizziness, *n* (%) | No | 50 (94.3%) |
| | Yes | 3 (5.7%) |

PLPH, post-lumbar puncture headache; Q, Quincke; W, Whitacre.

Table 3
Bivariate analysis of variables obtained from the active group

| | Complications<br>Raw OR (IC 95%) *p value* |
|---|---|
| Age | 0.942 (0.877–1.010)<br>0.099 |
| Gender | 0.137 (0.016–1.203)<br>0.059 |
| Male/Female | |
| Cognitive impairment | 0.319 (0.058–1.752)<br>0.256 |
| Yes/No | |
| Weight* | 0.995 (0.917–1.080)<br>0.914 |
| Intellectual disability | 1.172 (0.425–3.228)<br>0.252 |
| Headache history | 0.118 (0.055–0.249) |
| Yes/No | 0.020 |
| Needle type | 1.20 (0.252–5.709) |
| Whitacre/Quincke | 1.000 |
| Diameter | 1.190 (1.055–1.344) |
| 20Gauge/22Gauge | 1.000 |
| Position | 8 (1.508–42.448) |
| Lying down/Sitting | 0.021 |
| More than 1 attempt | 2.775 (0.548–14.059) |
| Yes/No | 0.340 |
| Volume | 1.002 (0.835–1.201)<br>0.986 |
| Hematic CSF | 3.900 (0.734–20.709) |
| Yes/No | 0.124 |
| Rest after procedure | 7.429 (3.729–14.798) |
| $\leq$1 h/>1 h | 0.151 |

*Weight data were obtained from 46 patients of the protocol group.

From the patients that suffered complications, intellectual disability was mild in 1 subject, moderate in 6, and severe in 1. The cognitive status of those subjects was DS-wCI in 6, DS-prodromal AD in 1, and DS-AD in 1.

We performed an exploratory analysis to study the association between the presence of complications and the recorded variables (Table 3). Age, weight, and intellectual disability degree did not show a statistically significant association with the occurrence of complications. In bivariate analysis, older subjects did show a lower risk of headache after the LP, but this effect was not present in the multivariate analysis. We also did not find any association between gender and the occurrence of complications. Previous history of headache showed a statistically significant association with the outcome in the bivariate analysis, but not in the multivariate regression analysis. The cognitive status did not affect the occurrence of complications. Among the variables related to the procedure, the patient positioning, needle type and diameter, number of attempts, volume of CSF extracted, hematic CSF, and rest after LP were not significantly associated with the presence of complications.

## DISCUSSION

Our study indicates that LP is a safe technique to evaluate CSF AD biomarkers in DS. In our global sample, 90% of the participants did not report any complication. When actively looking for them (*active* group), headache was the most frequent event, occurring in 9.4% of the subjects, but it was mild in most cases. Only 1 (1.9%) patient reported a typical PLPH that had a moderate severity and required treatment with a common analgesic drug. Dizziness and lumbar pain were other less frequent complications. No complication was reported in the clinical practice group.

Previous studies in the general population have reported headache prevalence after the LP ranging from 5% to 40% [17, 18, 22–30]. However, these studies used different methodologies. The frequency of complications differs in those studies using systematic protocols from those using data collected in the normal clinical practice [23, 26]. A recall bias might influence the absence of complications in this later group. Those studies in the general population that used the same systematic protocol from the Alzheimer's Association and the University of Gothenburg [17, 18] reported higher frequencies (36% and 31%) than that found in our study. Further-

more, the incidence of complications reported by our *active* group was significantly higher compared to the *clinical practice* group, where these complications were not actively searched. Consequently, it is not possible to rule out an infra-report of complications, mainly in the *clinical practice* group. This bias in the report of complications might be especially important in DS. Individuals with DS frequently present with unnoticed comorbidities. In many instances, when a medical comorbidity is found in a routine medical evaluation, neither the patient nor caregivers actively complain [31, 32]. The increased difficulty in reporting symptoms might be explained by the difficulties in language, especially in expressive language [33] and by the fact that many symptoms might be incorrectly associated with the syndrome itself and not with a new comorbidity. Difference in pain perception is another possibility that might account. There is a controversy about whether pain perception differs in individuals with DS from that in the general population. There are studies that suggest that subjects with DS have decreased sensitivity to pain [34], while others support that their sensitivity is increased [34, 35]. In any case, the difference of complications found between the *clinical practice* group and the *active* group supports the need to actively search for any medical condition in subjects with DS.

In our exploratory analysis, we did not find any variable that was significantly associated with the presence of complications after LP. The small sample size had probably limited the statistical power, demanding a cautious interpretation of these results. In this respect, the studies comparing pen-point needles with respect to cutting-edge needles have consistently found lower frequencies of headache in the atraumatic needles [24, 36, 37]. In addition to the small sample size, it is worth mentioning that we predominantly used the atraumatic pen-point needle (66% versus 34% with cutting-edge needle) in our sample. This pen-point needle is the one currently recommended for routine clinical practice and is now routinely used in our center [38, 39].

The main limitation of this study is the small sample size. The search for those factors associated with the presence of complications after the LP was limited by the small sample size in our study with respect to previous works [17, 18, 22, 23, 28–30]. However, this study gathered the largest sample of subjects with DS that have undergone a LP and it is the first study to address the feasibility of LP in individuals with DS in a systematic fashion. Other limitations are the fact that we did not systematically collect information regarding the amount of resting time after discharge and that we only asked the caregivers about the complications and not the subjects directly, which might have prevented finding a complication.

Our study supports the safety of LP in the study of AD in DS patients. The use of this technique in clinical research will enable the use of CSF AD biomarkers in DS to study the natural history of AD in DS and will enable earlier and better AD diagnosis in this population.

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