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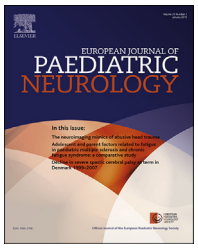

Original article

Increased cerebral microbleeds and cortical superficial siderosis in pediatric patients with Down syndrome

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ABSTRACT

Background: Patients with Down syndrome carry a third copy of the *amyloid precursor protein gene*, which is localized on chromosome 21. Consequently, these patients are prone to develop early-onset Alzheimer disease and cerebral amyloid angiopathy. Post-mortem studies suggest increased amyloid deposition to be already detectable in children with Down syndrome. The aim of our study was to evaluate if amyloid-related changes in pediatric Down syndrome patients can be detected *in vivo* using MRI biomarkers of cerebral microbleeds and cortical superficial siderosis.

Materials and methods: This retrospective study included 12 patients with Down syndrome (mean age = 5.0 years) and 12 age-matched control subjects (mean age = 4.8 years). Frequency and location of microbleeds and siderosis were assessed on blood-sensitive MRI sequences in a consensus reading by two radiologists applying a modified Microbleed Anatomical Rating Scale.

Results: Down syndrome patients showed a significantly higher mean microbleeds count and likelihood of siderosis than age-matched controls. Across groups, the highest microbleeds count was found in lobar regions (gray and white matter of frontal, parietal, temporal, and occipital lobes, and the insula), while fewer microbleeds were located in subcortical and infratentorial regions. The number of microbleeds increased over time in all three Down syndrome patients with a follow-up exam.

Conclusion: In vivo MRI biomarkers can support the diagnosis of early-onset cerebral amyloid angiopathy, which might already be present in pediatric Down syndrome patients. This might contribute to clinical decision-making and potentially to the development of therapeutic and

Abbreviation: CAA, Cerebral amyloid angiopathy; CMB, cerebral microbleeds; cSS, cortical superficial siderosis; DS, Down syndrome.

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prophylactic approaches, as cerebral amyloid angiopathy increases the risk for intracranial hemorrhage and may be associated with increased risk of developing Alzheimer disease.

1. Introduction

Down syndrome (DS) has moved into the focus of Alzheimer disease research as an early-onset model of the disease, as symptoms typically occur two to three decades earlier than in the general population.[1] The predisposition of DS patients to develop Alzheimer disease early in the course of life results from the presence of a third copy of the *amyloid precursor protein* gene on chromosome 21, which leads to increased amyloid levels[2] and ultimately to increased cerebral β-amyloid accumulation.[3] Elevated β-amyloid levels are already present in children and adolescents with DS,[4] and abnormally high amyloid accumulation has been reported in *post mortem* studies of DS patients as early as 8–12 years of age.[3,5]

Apart from early-onset Alzheimer disease, increased amyloid deposition might also manifest as cerebral amyloid angiopathy (CAA). In CAA, amyloid accumulation in the wall of small vessels leads to vessel damage, and ultimately rupture,[6,7] which results in cerebral microbleeds (CMB), cerebral superficial siderosis (cSS), and less frequently in lobar hemorrhage.[7] Post-mortem neuropathological studies in older DS patients have reported both, signs of CAA[3,8,9] and CAA-related intracranial hemorrhage.[10] The assumption that Alzheimer disease and CAA are endpoints of a common underlying process (i.e. increased amyloid deposition) in DS, is furthermore supported by the notion that CAA is found in almost all DS patients suffering from Alzheimer disease.[11] To date, it remains to be investigated whether CAA-related changes may already be present at earlier stages of the disease, in pediatric DS patients.

With the advent of T2*- and SWI MRI, CAA-related brain changes can be visualized *in vivo*.[12] Two imaging markers of CAA have been established. Firstly, CMB can be visualized as small dots of susceptibility-induced signal loss, which in CAA are primarily located in lobar brain regions.[13–15] Secondly, blood-sensitive MRI sequences can depict cSS as linear signal loss along the cortical surface, reflecting hemosiderin deposition in subpial layers of the brain, resulting from small vessel leakage into the subarachnoid space.[14] Signs of cSS can be regularly found in patients with CAA,[16–20] and are associated with higher risk for intracranial hemorrhage.[21,22] Association between the presence of cSS and CMB has been shown in patients with probable[23] and histologically proven[18] CAA.

In summary, DS patients are not only prone to develop early-onset Alzheimer disease; *post mortem* neuropathological studies suggest that increased amyloid levels might also put them at higher risk for developing early-onset CAA. Therefore, we aimed to evaluate the frequency and location of MR imaging markers of CAA to assess early signs of CAA-related changes in DS patients *in vivo*.

2. Methods

2.1. Study design and participants

This retrospective case–control study was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all patients. Patients were retrieved from our hospital-wide radiology information system. Inclusion criteria for the DS-patient and the control group comprised: age below 18 years, cranial MRI including blood-sensitive MRI sequences, and time of MRI between January 1, 2005 and September 1, 2015. For the exact search terms used please refer to the Supplemental information. The DS diagnosis was confirmed based on the electronic patient record. To increase the sample size of the DS patient group, we initiated a cooperation with the Istituto Giannina Gaslini children's hospital in Genoa, Italy. Following the same inclusion criteria, MRI scans were selected from their electronic database, anonymized and transferred to our picture archiving and communication system to allow for a standardized assessment. If available, follow-up MRI exams were included to evaluate evolution of CMB and cSS over time.

For the selection of the age- and sex-matched control group, we included pediatric patients (without the diagnosis of DS) who underwent an MRI including blood-sensitive MRI sequences (which are not part of the clinical routine protocol). Absence of structural alterations on conventional MRI sequences (excluding the blood-sensitive sequences), as determined by a neuroradiological reading, was defined as an additional inclusion criterion.

2.2. Image acquisition and analysis

MRI exams from different scanners applying different blood-sensitive sequences (T2*, T2WI/FFE, or SWI) were included. Most scans were acquired using 1.5 TS MRI scanners (Siemens Medical Solutions, Erlangen, Germany). TE ranged from 16 to 50 ms (median = 23) and slice thickness from 1.5 to 5.0 mm (median = 4.0). For detailed information please see Supplementary Table 1.

Images were analyzed by two radiologists with 2 and 20 years of experience in neuroradiology, respectively, based on a modified Microbleed Anatomical Rating Scale.[24] This scale provides good intra- and inter-reader reliability for the detection of CMB in all brain regions, even when based on different MRI sequences and levels of experience.[24] To increase sensitivity, we chose to conduct a consensus reading. In case of discrepant initial readings, the MRI was reevaluated and a consensus rating was reached upon discussion. The two radiologists were blinded with respects to the patient's status (diagnosis of DS vs. non-DS).

CMB were defined as small, round, well-defined, hypointense lesions on T2*/SWI, which measure between 2 and

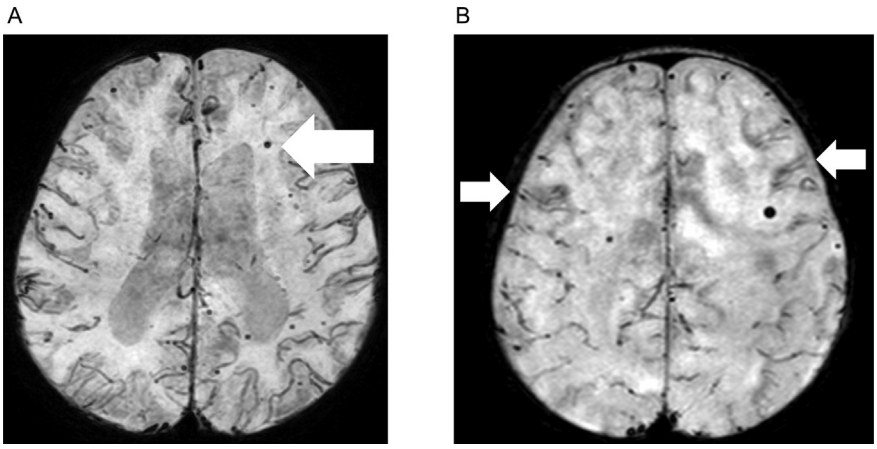

Fig. 1 – A: The susceptibility-weighted (SWI) sequence of the cranial MRI of a male Down syndrome patient (age: 1 year, 8 months) shows multiple cortical and subcortical lobar cerebral microbleeds, the white arrow points to an exemplary microbleed in the left frontal lobe. B: Biparietal cortical superficial siderosis (as indicated by white arrows) and multiple microbleeds in a male Down syndrome patient (age: 1 year, 8 months), susceptibility-weighted (SWI) sequence of the cranial MRI.

10 mm and are hard to identify on T2WI[24] (see Fig. 1A). Typical CMB mimics, such as diffuse axonal injury, hemorrhagic micro-metastases, hemorrhagic brain insults as well as cavernomas were excluded based on T1w and T2w images, in combination with available medical records.

CMB were evaluated in three main regions (infratentorial, deep, and lobar) for each hemisphere separately. Infratentorial subregions included brainstem and cerebellum. Deep regions included basal ganglia, thalamus, internal and external capsule, corpus callosum, and periventricular white matter. Lobar brain regions consisted of gray and white matter of frontal, parietal, temporal, and occipital lobes, and the insula.

The evaluation of cSS, which was defined as a linear, hypointense pattern that follows the gyri in blood-sensitive MRI sequences[25] (see Fig. 1B). The presence of cSS in each subregion was rated as a binary variable with a maximum of 21 possibly affected subregions (N = 11 deep, N = 10 lobar). Infratentorial regions were not rated for cSS.

2.3. *Statistical analysis*

Data are presented as means ± standard deviation or medians with interquartile range, where appropriate. Between-group differences in mean CMB count were analyzed with the *t*-test for two independent samples. Potential influence of group, age, and sex on mean CMB count was assessed in a multivariate analysis. The level of significance was set at $\alpha = 0.05$. For statistical analysis IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. (2011) was used.

3. Results

3.1. *Participants*

N = 10 pediatric DS patients fulfilled inclusion criteria. Our Italian research partner contributed N = 3 patients to the DS patient group, resulting in a total of N = 13 DS patients. One DS patient had to be excluded due to a post-ischemic periventricular white matter lesion, to avoid overlap between CMB and white matter injury of prematurity. Follow-up exams were available for N = 3 DS patients, allowing for the evaluation of CMB and cSS over time with a median follow-up time of 16 months (range: 4–54

Table 1 – Overview about patient characteristics by group.

Patient characteristics	DS patient group N = 12	non-DS control group N = 12
Demographics		
Age at time of scan in years	5.0 ± 5.1	4.8 ± 3.8
Female	6 (50)	7 (58)
Preterm birth (28–33 weeks of pregnancy)	5 (42)	4 (33)
Additional diagnoses		
Congenital heart disease	6 (50)	1 (8)
Developmental delay/disorders	1 (8)	10 (83)
Seizures	3 (25)	6 (50)
Hydrocephalus	2 (17)	0 (0)
Developmental venous anomaly	1 (8)	0 (0)
Small postischemic lesion in the right		
MCA territory	1 (8)	0 (0)
History of meningitis	1 (8)	0 (0)
Possible CMB mimics based on history		
Significant traumatic brain injury/ diffuse axonal injury	0 (0)	0 (0)
Malignancies	0 (0)	0 (0)

Age is presented as mean and standard deviation, the other variables are shown as frequencies and percentages: N (%).
CMB = cerebral microbleeds, DS = Down syndrome, MCA middle cerebral artery.

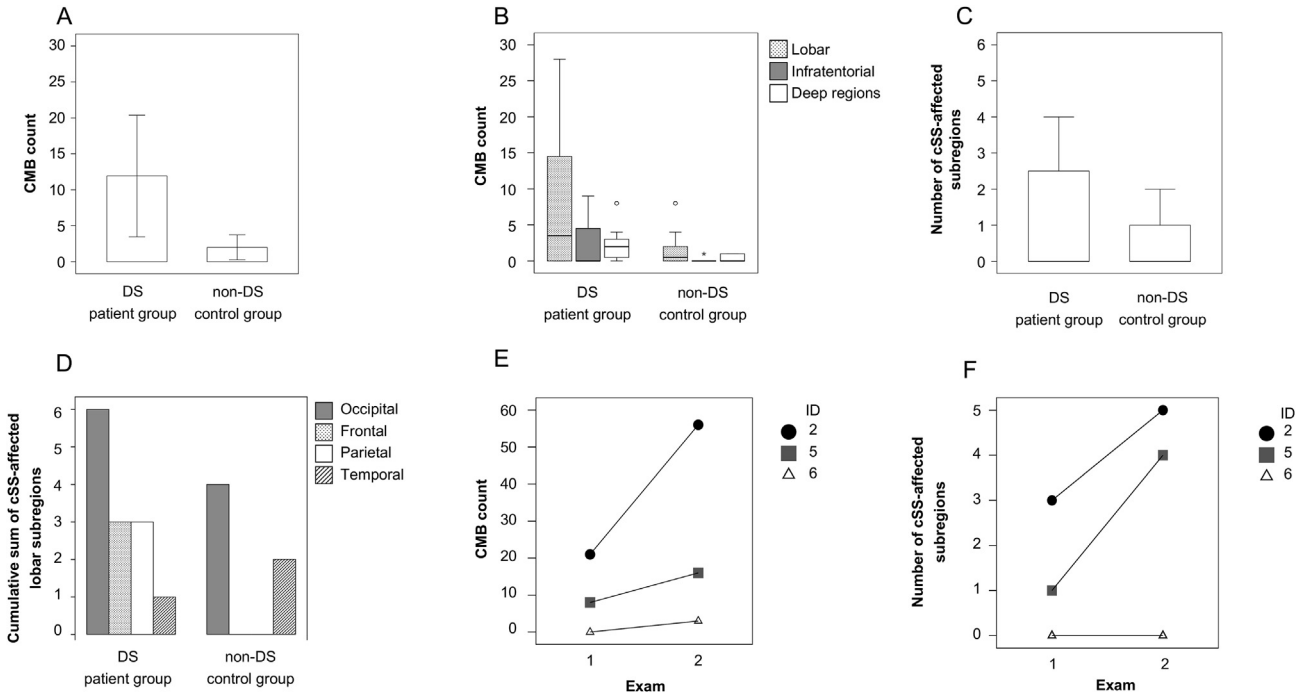

Fig. 2 – A Cerebral microbleeds (CMB) count with mean and 95% CI (y-axis) for the Down syndrome (DS) patient group and the non-DS control group (x-axis). B Total CMB count with median, interquartile range (y-axis) by lobar, infratentorial and deep brain regions comparing DS patient group and non-DS control group (x-axis). C Number of cortical superficial siderosis (cSS)-affected subregions with median, interquartile range (y-axis) by DS patient and control group (x-axis). D Cumulative sum of cSS-affected lobar subregions (y-axis) by DS patient and control group (x-axis). E CMB count of DS patients (y-axis) at the time of the first and the follow-up exam (x-axis). F Number of cSS-affected subregions (y-axis) at the time of the first and the follow-up exam (x-axis).

months). The first 12 consecutive age-matched non-DS patients who fulfilled all eligibility criteria were included in the control group. Table 1 provides an overview of patient characteristics (please see Supplementary Table 2 for more details).

3.2. *Down syndrome patients showed significantly more cerebral microbleeds*

In the DS patient group 75% (N = 9) were affected by CMB, versus 58% (N = 7) in the non-DS control group. DS patients had a significantly higher mean CMB count (11.92 CMB ± 13.311) than non-DS patients (2.0 ± 2.730 SD), P = 0.019 (See Fig. 2A). A multivariate model to predict the total CMB count identified the group as an independent predictor (P = 0.025), while sex (P = 0.490) and age (P = 0.477) did not show a significant effect on the total CMB count.

3.3. *Cerebral microbleeds were predominantly located in lobar subregions*

Most CMB of DS patients were found in lobar regions (65% of CMB), 18% in deep regions, and 16% in infratentorial regions; median CMB count in lobar regions = 3.5, interquartile range (IQR) = 15, see Fig. 2B. In the control group, the median was much lower: 0.5 (IQR = 2) with a total of N = 6 patients being affected. CMB in deep regions were found in N = 9 (75%) of the DS patients (median = 2, IQR = 3), while only N = 5 (42%) of the control group had CMB in this region (median = 0, IQR = 1). The infratentorial region was least affected in both groups. N = 4 (33%) of the DS patients had infratentorial CMB (median = 0, IQR = 5). In the control group, only one patient was affected, and presented with a single infratentorial CMB. For a detailed description of CMB and cSS distribution in all patients of both groups, please refer to Supplementary Table 3.

3.4. *DS patients were more likely to show cortical superficial siderosis*

In the DS-patient group 42% (N = 5) were affected by cSS, versus only 25% (N = 3) in the control group. The median count of cSS-affected subregions (out of N = 21 possibly affected supratentorial regions did not differ between groups (median = 0). However, the 75th percentile and the maximum number of cSS-affected subregions were higher in the DS patient group (IQR 0–2.75, maximum = 4) than in the control group (IQR 0–1.5, maximum = 2), see Fig. 2C.

We analyzed the distribution of cSS within the 10 lobar subregions according to the modified Microbleed Anatomical Rating Scale. The cumulative sum of cSS for each lobar subregion by group shows an occipital predominance of the cSS with a higher cumulative sum of occipital cSS in the DS patient group (N = 6) than in the control group (N = 4, see Fig. 2D).

All patients from both groups with cSS also had at least one CMB. There were significantly more CMB in DS patients with cSS (mean = 22.0 ± 13.78) than in DS patients without cSS

(mean = 4.7 ± 7.27, p = 0.017). Non-DS patients with cSS had a mean CMB count of 5 ± 4.0. In each group, N = 4 patients with CMB were not affected by cSS.

3.5. *Evolution of cerebral microbleeds and cortical superficial siderosis over time*

All three patients with available follow-up exams showed an increase of CMB count over time. In the first patient (ID 2; see Fig. 2E) the CMB count increased from N = 21 to N = 56 in 4.5 years. In the second patient (ID 5) the CMB count doubled from N = 8 to N = 16 in 4 months. The third patient (ID 6) did not show any CMB on the first, but N = 3 CMB at 16-months follow-up. Regarding cSS-affected subregions, both affected subjects showed an increase (from N = 1 to N = 4 and from N = 3 to N = 5, respectively), while the third patient (ID 6) was not affected by cSS at all (see Fig. 2F).

4. Discussion

In the present study, we assessed signs of CMB and cSS in pediatric DS patients *in vivo* applying blood-sensitive MRI techniques. We found that pediatric DS patients show a significantly higher amount of CMB and are more often affected by cSS than age-matched non-DS patients. Regarding the spatial distribution, CMB were predominantly located in lobar brain regions. Within lobar regions cSS was predominantly located in the occipital lobe. Additionally, our results point to an increase of CMB and cSS-affected subregions over time.

4.1. *Our findings might indicate early CAA in DS*

Lobar predominance of CMB and concomitant cSS - as detected in DS patients in this study - have been described as MRI markers of CAA.[13,26] It has been proposed that high amyloid levels in DS patients might lead to amyloid accumulation in the wall of small vessels.[2,27,28] *Post mortem* studies have confirmed signs of CAA in older DS patients.[3,8,9] Here, we could show that CAA-related changes might already be present at earlier stages of the disease, in pediatric DS patients. Although, according to the Boston criteria,[12] CAA typically occurs at a later age, the genetic predisposition of DS patients may put them at risk of developing CAA much earlier.

Although alternative etiologies for CMB and cSS in DS patients should be considered (see below), several observations support the interpretation of CMB and cSS as results of CAA as a common underlying cause. First, lobar predominance of CMB and cSS in our DS patient group is in line with previous results of lobar predominance of CMB[12,29,30] and cSS[30] in CAA patients. Within lobar regions, the occipital lobe (described as a region that is more prone to develop amyloid deposits than others[31]) has been reported to be most frequently and severely affected by CAA.[6,32,33] Second, concomitant presence of CMB and cSS points toward a common underlying cause, as has been shown in CAA[34] and AD.[35] However, other studies found that CMB and cSS do not necessarily occur simultaneously in CAA.[19,20] Third, progression of CMB and cSS over time, as shown in adult patients with CAA,[29] points towards a common neuropathological mechanism. However, alternative etiologies of the observed CMB and cSS in children with DS should be considered. Most importantly, co-morbidities such as congenital heart defects, which were present in 50% of our DS patients, have to be taken into account.

4.2. *Clinical relevance of increased CMB and cSS-affected subregions in pediatric DS patients*

Our results point towards early CAA-related changes in DS patients. The possibility of *in vivo* detection of MRI biomarkers of CAA in DS patients, who are at risk of developing CAA at an early age, could be of great clinical relevance. Most importantly, the occurrence of CMB, cSS and CAA is associated with an increased risk of intracranial hemorrhage.[36–40] This poses clinical challenges especially regarding potential implications the use of antithrombotic therapy (for review, see [4; 5]). Therefore, anti-coagulation therapy, which might be necessary in the context of congenital heart disease and surgical correction in DS patients,[41] should only be initiated after careful consideration of potential risks and benefits.[13] Furthermore, thrombocyte activation inhibitors, such as acetylsalicylic acid, which are also commonly used as pain medication, might need to be avoided.

Increase of CMB and cSS over time might also imply a progression of the underlying disease, and therefore increased risk of intracranial hemorrhage, cognitive impairment, and mortality.[15] However, before any clinical recommendations (e.g. regarding follow-up exams if CMB and cSS have been identified) can be made, prospective research needs to be done. *In vivo* MRI biomarkers would provide a valuable tool for the longitudinal follow-up of DS patients from a very young age on. This non-invasive approach may contribute to a better understanding of brain changes due to β-amyloid accumulation over the course of the disease.

4.3. *Limitations*

The generalizability of our findings is limited by the relatively small sample size. By pooling data from two large university hospitals, we were aiming to provide first insights, that might set the stage for larger, prospective studies. Furthermore, as this was a retrospective study of routinely acquired MRI data, there was some variation in the image acquisition (scanner, sequences) and the control group consisted of non-DS patients, who were scanned for a clinical indication. Our finding that more than 50% of the control group showed CMB – which is considerably above what would be expected in healthy adults,[13] albeit significantly lower than in our DS cohort – should be interpreted in this context. For example, one of the patients in the control group had a congenital heart disease, that could lead to CMB.[42,43] Although studies on CMB in pediatric patients are scarce, the preliminary findings point to the absence of a clear systemic anatomic distribution of CMB in pediatric patients after heart surgery[42] (as opposed to the preliminary lobar distribution observed in our study). As some of the DS patients had a history of a congenital heart disease, one may argue that this could

explain at least some of the CMB among DS patients. However, we are not aware of any studies reporting on cSS alongside with CMB in patients with congenital heart disease or after cardiac interventions. Thus, the co-existence of cSS supports the hypothesis of CAA as a common etiology in this patient group.

Additionally, most non-DS control patients had developmental delays, and half of them suffered from seizures, which might have contributed to the higher CMB count as well (please see Table 1). In general, there is very little evidence on the prevalence of CMB in developmental delay and epilepsy. Apart from a case report on CMB in two patients with refractory status epilepticus,[44] systematic evaluation remains to be conducted. However, our study design with a control group of non-DS patients is likely to underestimate, rather than to overestimate the true difference of CMB between pediatric DS patients compared to (healthy) non-DS children. Interpreting the number of CMB counts in the non-DS control group is also challenging, as data on the incidence of CMB in healthy children is lacking. Theoretically, the rate of CMB could be generally higher in healthy children than in adults due to a higher frequency of subconcussive head injury/mild traumatic brain injury in the pediatric population.[45] Some of the limitations outlined above could by addressed by increasing the sample size or by performing a longitudinal follow-up study for a smaller group (thus, limiting potential confounders) and using a more homogeneous control group for comparison.

5. Conclusion

Our findings indicate an increased prevalence of MRI biomarkers of CAA in pediatric DS patients. This may have implications for patient management, especially regarding the potentially increased risk of intracranial hemorrhage. Also, early signs of CAA may be an indicator for a generally high cerebral amyloid burden, which is known to result in early-onset AD in DS patients. *In vivo* imaging of neuropathological changes in DS patients could foster our understanding of early phases of CAA and AD and, thus, contribute to the development of preventive and therapeutic concepts. We hope that the results of this pilot study may set the stage for future prospective studies that investigate the association between CAA and AD in DS patients.

Conflicts of interest

The authors declare no conflict of interest relevant to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.09.004.

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