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The pimple sign of progressive supranuclear palsy syndrome

Hugo Botha [a], Jennifer L. Whitwell [b], Ajay Madhaven [b], Matthew L. Senjem [c], Val Lowe [b], Keith A. Josephs [a,*]

[a] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[b] Department of Radiology, Mayo Clinic, Rochester, MN, USA
[c] Department of Information Technology, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Background: Some patients with progressive supranuclear palsy syndrome (PSPS) demonstrate a focal area of midbrain hypometabolism on FDG-PET scans which we call the 'pimple sign'. We assessed its association with midbrain atrophy, its reliability and its ability to differentiate PSPS from corticobasal syndrome (CBS) and multiple system atrophy (MSA).
Methods: We identified 67 patients with PSPS, CBS or MSA who had volumetric MRI as well as FDG-PET imaging. Midbrain volume was measured and expressed as a percentage of total intracranial volume. Two independent, blinded specialists rated the 'pimple sign' on FDG-PET as 'absent', 'possible' or 'definite'. Midbrain volumes were compared across these groups and reliability assessed with the kappa statistic. Sensitivity and specificity were calculated using CBS and MSA patients as controls.
Results: Midbrain volume was decreased in the 'definite' group compared to the 'absent' and 'possible' groups ($p = 0.0036$). Inter-rater reliability for the pimple sign was high ($\kappa = 0.90$). A 'definite pimple sign' had a high specificity (100%) but low sensitivity (29%) for PSPS, whilst the presence of a possible or definite sign had a sensitivity of 79%.
Conclusion: The 'pimple sign' of PSPS is associated with midbrain atrophy, and may be helpful in differentiating PSPS from CBS and MSA.

1. Introduction

Progressive supranuclear palsy (PSP) is a chronic, progressive neurodegenerative disorder characterized pathologically by the accumulation of abnormal tau protein [1]. In its typical form, PSP syndrome (PSPS), it manifests clinically with postural instability, vertical supranuclear gaze palsy, axial rigidity and dysarthria, although a large spectrum of other presentations can be associated with PSPS [2]. Diagnosing PSPS can be very challenging, especially given the significant overlap with other atypical parkinsonian disorders [3]. In addition to the need for accurate diagnosis and prognosis, differentiating it from other degenerative disorders will become increasingly important as disease modifying treatments become available.

Neuroimaging can aid in the early diagnosis of PSP. Magnetic resonance imaging (MRI) findings that have been described in PSPS include atrophy of the midbrain, superior cerebellar peduncle and frontal lobes [4,5]. Midbrain atrophy can often be seen on visual inspection, as the "hummingbird sign" on sagittal view of the brainstem [6]. Several midbrain-related indices, involving midbrain diameter, area and volume have been described, with varying clinical utility [7,8].

Positron emission tomography (PET) imaging with 18F-fluorodeoxyglucose (FDG) has been shown to be helpful in differentiating among parkinsonian disorders. Characteristic metabolic abnormalities in PSPS include hypometabolism of the brainstem and midline frontal structures, although brainstem hypometabolism has been observed in corticobasal degeneration (CBD) or multiple system atrophy (MSA) [9]. Midbrain hypometabolism could be a promising early marker of PSPS, but isn't readily apparent on visual inspection of conventional PET images [10]. Several software packages allow for the creation of metabolic maps for each patient using Z-scores, after which metabolism can be assessed visually, and CortexID is used at our institution [9]. The use of such automated statistical analyses has made FDG-PET a more feasible clinical tool, and increases the sensitivity and specificity of FDG-PET [9,11].

We have noticed a focal area of midbrain hypometabolism on CortexID FDG-PET scans in some patients with PSPS and have

* Corresponding author. Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA. Tel.: +1 507 538 1038; fax: +1 507 538 6012.
E-mail address: josephs.keith@mayo.edu (K.A. Josephs).

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named this the 'pimple sign'. It is unclear, however, how this relates to midbrain atrophy, as prior research suggests midbrain hypometabolism is present early, doesn't progress as much as other areas of hypometabolism and doesn't correlate with clinical deterioration, whereas it is clear that midbrain atrophy progresses in a near-linear fashion in PSPS and correlates with disease progression [10,12]. Whether the pimple sign is indicative of midbrain atrophy or associated with PSPS has not been established. Our primary objective was to assess whether the pimple sign is associated with midbrain atrophy. Our second objectives were to determine inter-rater reliability of the sign and to assess whether the pimple sign is associated with PSPS.

2. Methodology

2.1. Subjects

The Mayo Clinic Medical Records Linkage system was queried to identify all patients seen in the Department of Neurology between January 1, 2005, and September 30, 2012 who had a clinical diagnosis of PSPS, CBS or MSA and had both volumetric MRI as well as FDG-PET imaging done within 12 months of each other. The following search terms, along with their abbreviated versions, were used: *progressive supranuclear palsy*, *Richardson syndrome*, *Steele–Richardson–Olszewski syndrome*, *multiple system atrophy*, *multisystem atrophy*, *corticobasal degeneration*, *corticobasal ganglionic degeneration* and *corticobasal syndrome*. A total of 89 patients were identified. Patients were retrospectively diagnosed at the time they were imaged, according to the NINDS-SPSP criteria for PSPS [13], the criteria for CBS [14] and the criteria for MSA [15]. Patients where the diagnosis was strongly suspected clinically but where patients didn't meet criteria for any of the disorders at the time of their scans were excluded. Cases which met criteria for both possible PSPS and CBS were designated as possible PSPS (7 patients) given the high specificity of the NINDS-SPSP criteria [16]. Twenty-two patients were excluded because they did not meet criteria for PSPS, CBS or MSA at time of imaging. The clinical records of the remaining 67 patients were reviewed to extract clinical data, including age at onset, age at scan, sex, initial presenting symptoms, dates of MRI and PET imaging.

The study was approved by the Mayo institutional review board.

2.2. FDG-PET imaging

All PET scans were acquired using a PET/CT scanner (GE Healthcare) operating in 3D mode. Subjects were injected with fluorodeoxyglucose in a dimly lit room with minimal auditory stimulation. An 8-minute FDG scan was performed after a 30-minute uptake period, which consisted of four 2-min dynamic frames following a low dose CT transmission scan. Standard corrections were applied and frames were realigned if motion was present. We used the CortexID (GE Healthcare) software package and ran an automated analysis using 3D stereotactic surface projections [17]. Activity for each subject's scan was normalized to the pons and compared to an age-segmented normative database. The program provides 3D stereotactic surface projection images with a metabolic map using the Z-scores as calculated for each surface pixel. The midsagittal images were extracted for analyses since we were interested only in the midbrain. Two experts (KAJ and JLW), blinded to patients' clinical information as well as midbrain data, independently rated the scans as showing an 'absent', 'possible' or 'definite' pimple sign (See Fig. 1). Grading was done focusing only on that one area independent of hypometabolism elsewhere throughout the brain. Their responses were recorded and discordant cases were discussed and a consensus reached.

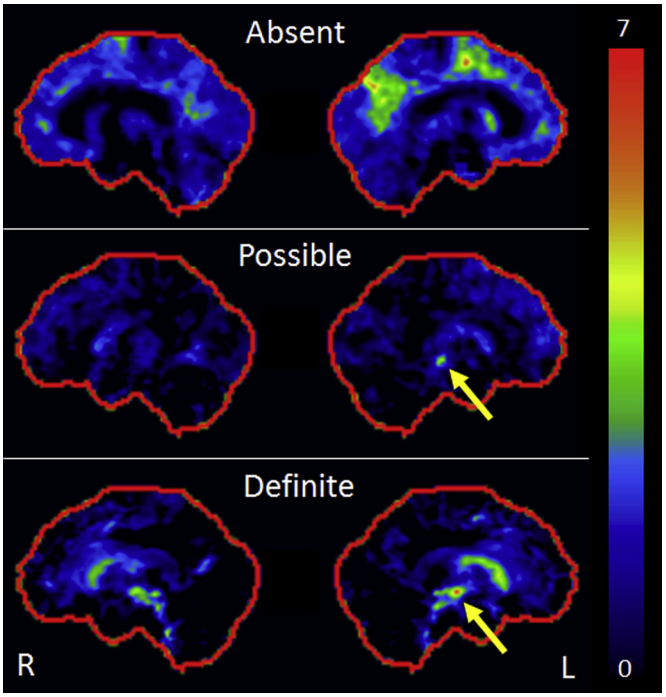

Fig. 1. FDG-PET imaging showing examples of 'absent', 'possible' and 'probable' pimple signs.

2.3. Volumetric MRI

All patients had a volumetric MRI performed with a standardized protocol, as previously described [18]. Midbrain volume was measured for each scan by propagating a template-drawn midbrain volume mask into the native space of each patients scan. Midbrain volume was manually traced on a customized template in Analyze software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) according to previously published guidelines [19]. Total intracranial volume (TIV) was measured on each scan by propagating a template-drawn TIV mask to subject space using SPM5. Midbrain volume was divided by TIV (MB/TIV) in order to correct for differences in head size across subjects [20].

2.4. Statistical analysis

JMP Pro Version 9.0.3 (SAS Institute Inc, Cary, NC, USA) was used for all the statistical analyses, with alpha set at 0.05. One-way ANOVA was computed using the MB/TIV variable across the 'absent', 'possible' and 'definite' groups, and since this showed statistical significant differences, comparison of each pair using Student's t was computed. The Bonferroni correction for multiple comparisons was applied. Inter-rater reliability was assessed with the kappa statistic. The sensitivity and specificity of a 'definite' as well as 'possible' pimple sign were assessed by using possible and probable PSPS patients as cases and all other diagnoses as controls. Likelihood ratios were computed, correcting for empty cells in the 2×2 table by adding 0.5 to all cells [21].

3. Results

3.1. Patient characteristics

Demographic characteristics are summarized in Table 1 and the final diagnoses in Table 2. Of note, among the three groups

Table 1
Patient demographics and MRI findings.

	Pimple sign grading			*P* value
	Absent	Possible	Definite	
Male/female	10/18	13/15	8/7	0.11
Age at onset, years	64.4 (61.1–67.7)	64.1 (60.7–67.4)	66.5 (61.2–71.7)	0.74
Age at scan	67.6 (64.3–70.8)	67.5 (64.3–70.8)	70.7 (65.5–75.9)	0.55
PSP	73.3 (67.7–78.9)	66.3 (62.7–69.9)	70.7 (66.2–75.1)	0.09
CBS	66.4 (61.8–71.1)	69.3 (63.4–75.3)	N/A	0.44
MSA	61.2 (48.9–73.5)	N/A	N/A	N/A[a]
Disease duration at scan, years[a]	3.2 (2.3–4.0)	3.5 (2.6–4.3)	4.2 (2.9–5.6)	0.40
PSP	3.1 (1.4–4.8)	3.2 (2.1–4.3)	4.2 (2.8–5.7)	0.46
CBS	2.6 (1.8–3.5)	4.0 (2.9–5.1)	N/A	0.051
MSA	6.2 (4.1–8.3)	N/A	N/A	N/A[a]
Midbrain volume (MB) (mm^3)	7629 (7223–8030)	7341 (6938–7744)	6977 (6334–7621)	0.22
Total intracranial volume (TIV) (cm^3)[b]	1423 (1370–1476)	1434 (1381–1488)	1497 (1412–1582)	0.33
MB/TIV (%)	0.54 (0.52–0.56)	0.51 (0.49–0.53)	0.47 (0.43–0.50)	0.004

[a] ANOVA not possible.
[b] Expressed as cm^3, analyses run in mm^3.

classified by the pimple sign ('absent', 'possible' and 'definite') there were no significant differences in age of onset or duration of illness at time of scan. Of the 38 patients diagnosed with PSPS, 18 met criteria for possible PSPS, with 8 patients demonstrating vertical supranuclear gaze palsy but not having experienced falls within the first year of disease onset and 10 patients having experienced falls with slowing of saccades but no gaze palsy. Of the remaining cases, 20 had probable PSPS, of which 3 patients later had pathological confirmation of PSP on autopsy, and were hence diagnosed with definite PSPS. Given the criteria used and the exclusion of patients not meeting these criteria despite a suspicion of PSPS, our patients all had the classic variant (Richardson's syndrome) of PSPS. Two of the three MSA patients had MSA-P and the other one had MSA-C. Seven patients had expired without autopsy.

3.2. Imaging findings

Imaging data is summarized in Tables 1 and 2. Mean duration between FDG-PET and MRI imaging was 28.4 days (11.1–45.7). There were 11 patients judged to have a 'definite' pimple sign, 28 with 'possible' pimple signs and 28 with 'absent' pimple signs. ANOVA among the groups showed a significant difference in MB/TIV between groups (*F*-ratio 6.161, Prob > *F* 0.0036). Comparison of each pair with Student's *t*-test showed significant differences in MB/TIV for the 'absent' compared to 'definite' and 'possible' compared to 'definite' groups, but after Bonferroni correction only the 'absent' compared to 'definite' pair retained statistical significance ($p = 0.0009$). Of note, there was a large degree of overlap in the MB/TIV among groups, as can be seen in Fig. 2.

Table 2
Pimple sign grading across diagnostic groups.

	Pimple sign grading			Total
	Absent	Possible	Definite	
PSPS[a]	8	19	11	38
(possible)	*5*[b]	*8*[b]	*5*[b]	*18*[b]
(probable)	*3*[b]	*9*[b]	*5*[b]	*17*[b]
(definite)	0[b]	*2*[b]	*1*[b]	3[b]
CBS	17	9	0	26
MSA	3	0	0	3
Total	28	28	11	67

PSPS = progressive supranuclear palsy syndrome; CBS = corticobasal syndrome; MSA = multiple system atrophy.
[a] Diagnostic classification at time of scan, with the exception of 'definite' which includes post mortem data.
[b] Not tallied towards total.

3.3. Reliability and utility of the pimple sign

The two raters agreed on all but 4 of the PET scans, and for these cases a consensus was reached. Inter-rater reliability assessment with the kappa statistic revealed 'very good agreement' (kappa = 0.90, 95% CI 0.82–1.00). All of the 11 patients deemed to have a 'definite' pimple sign met diagnostic criteria for PSPS (5 possible, 5 probable and 1 definite). Only 8 of the 38 PSPS patients had 'absent' pimple signs (5 possible, 3 probable). Comparing PSPS to CBS and MSA, a 'definite' pimple sign had a sensitivity of 28.95% (15.98–46.11%) and a specificity of 100% (85.44–100%) with a corrected [21] positive likelihood ratio of 18 (1.09–288) and a negative likelihood ratio of 0.72 (0.58–0.88). There was a substantial overlap in the patients with a 'possible' pimple sign, with 17 out of 38 patients with PSPS and 11 out of 29 patients with another diagnosis having a 'possible' pimple sign. The sensitivity and specificity of any pimple sign ('possible' or 'definite') being present was 78.95% (62.22–89.86%) and 68.97% (49.05–84.02%), respectively, with a

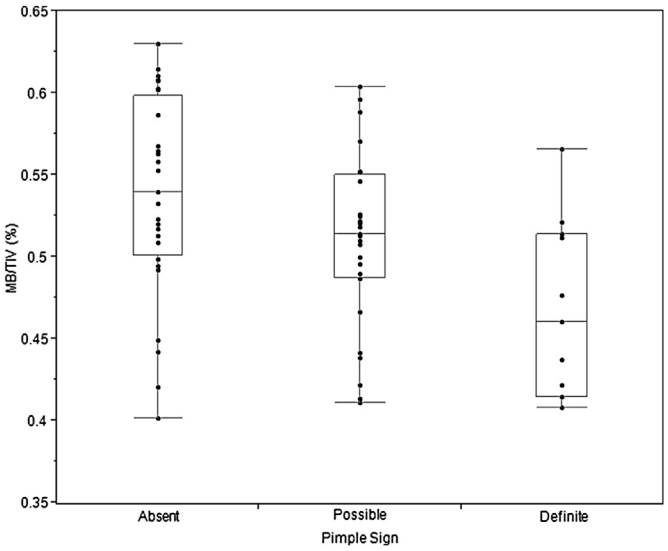

Fig. 2. Corrected midbrain volumes across the three pimple sign groups.

positive likelihood ratio of 2.54 (1.44–4.48) and a negative likelihood ratio of 0.31 (0.16–0.59).

4. Discussion

The present study describes the 'pimple sign' of PSPS, a focal area of midbrain hypometabolism evident on FDG-PET imaging. Of note, our findings are limited to the Richardson's syndrome variant of PSPS, but we will use the term PSPS owing to the fact that much of the prior work in this area did not differentiate between PSPS subtypes. The mean corrected midbrain volume of patients with a 'definite' pimple sign was significantly less than those of patients with an 'absent' pimple sign. Although not significant after Bonferroni correction, there was a trend towards a smaller corrected midbrain volume among cases with a 'possible' pimple sign compared to an 'absent' pimple sign, and between cases with a 'definite' pimple sign and a 'possible' pimple sign. We also found the pimple sign to have a very high inter-rater reliability and high specificity for distinguishing between PSPS and CBS/MSA.

Establishing a diagnosis of PSPS on clinical grounds alone is difficult, especially early in the course of the disease, with some estimates placing the time from symptom onset to diagnosis at up to three years [13,22]. Furthermore, patients presenting initially to non-neurologists might experience a greater delay. Since there is a large degree of overlap between the parkinsonian disorders differentiating between them is crucial [22]. Neuroimaging has been proposed as a means for differentiating among these disorders, and specifically, for separating PSPS from other atypical parkinsonian disorders [9,23].

Several researchers have evaluated the role of structural imaging in the diagnosis of PSPS, and signs of midbrain atrophy on conventional MRI evident on visual inspection include the 'hummingbird sign' on midsagittal view and the 'morning glory flower sign' on axial views [6]. Quantitative measures of midbrain atrophy include the AP diameter [23], midbrain area [4], the ratio of midbrain and pontine area [7,8] and the 'MR parkinsonism index' [8], calculated as the pontine-to-midbrain area ratio multiplied by the middle to superior cerebellar peduncle width ratio. These have been found to be most helpful in differentiating PSPS from controls and PD, and inconsistently, MSA. Studies of VBM in PSPS have shown significantly smaller midbrain volumes compared to controls [24–27]. Midbrain volume was also shown to separate PSP from CBD at a group level [24] and PSPS from CBS [26] but not on an individual patient basis with sufficient sensitivity and specificity [28]. Other researchers evaluating midbrain volume or area as a percentage of total intracranial volume (MB/TIV) [4,28] found this was significantly decreased in the PSPS group. Although not the primary aim of this study, our MB/TIV results among patients with PSPS are similar as reported previously.

We have demonstrated that the pimple sign is associated with midbrain atrophy expressed as the MB/TIV ratio at a group level. As others have pointed out [29], several of the metabolic abnormalities on FDG-PET in PSPS patients could represent neuronal cell loss rather than a primary phenomenon from which neuronal death follows, since patients are often studied in an advanced stage. However, midbrain hypometabolism has also been reported early in PSPS [10]. Whilst midbrain atrophy as measured by the MB/TIV variable seems to correlate with progression of gait/midline impairment, executive dysfunction, and ocular motor impairment [12], midbrain hypometabolism might be independent of clinical deterioration [10]. Although the association between midbrain atrophy and a positive pimple sign in the current project would support the hypothesis that hypometabolism is the result of neuronal loss, there was a significant overlap among groups. As is clear from Fig. 2, several patients with an absent pimple sign had considerable atrophy whilst others had a positive sign with maintained midbrain volumes. Furthermore, we did not find any difference in the mean duration of illness between patients with and without the pimple sign, as one might have expected given the linear progression of midbrain atrophy. These findings provide evidence for a true metabolic deficit out of keeping with the neuronal loss underlying the pimple sign, and may indicate that the pimple sign could be found early in the disease course among some patients.

The association between the pimple sign and a clinical diagnosis of PSPS is consistent with prior work on the use of FDG-PET in the diagnosis of PSPS. Several small studies compared PSPS to controls and found midbrain hypometabolism to be a defining feature of the PSPS group [10,30–32]. However, as Litvan et al. [16] and others have pointed out, a useful diagnostic sign would ideally differentiate PSPS from other disorders resulting in parkinsonism and cognitive or behavioral problems. In this regard, midbrain hypometabolism was found in PSPS compared to PD [11,33], MSA [11,33] and CBS [11,31].

These comparisons were predominantly evident on a group level, whereas demonstrating the ability of FDG-PET to classify individual patients would be more instructive clinically. Furthermore, it's worth noting that midbrain hypometabolism is often not evident on visual inspection of conventional scans [9,10]. Eidelberg and colleagues [9] sought to address these concerns by creating disease specific metabolic maps for the parkinsonian disorders from FDG-PET data. Midbrain and midline frontal hypometabolism were defining features for PSPS, and their maps allowed a non-expert reader to correctly classify 92.4% of parkinsonian disorders on an individual patient basis. The low sensitivity of a definite pimple sign would limit its use as an independent diagnostic tool, in that many patients would still be unclassified based on the absence of a definite pimple sign, but the high specificity may be clinically useful. The sign would be most useful when used in conjunction with other imaging findings, which are often specific but lacking in sensitivity. Furthermore, sensitivity of either possible or probable sign approaches 80%, and so the absence of *any* pimple sign is evidence against PSPS. Several of the conventional MRI findings mentioned above require advanced measurements or calculations, and on an individual basis the sensitivity and specificity is only moderate [34]. The automated analyses employed here are simpler, and the specificity of the sign is very high when classifying individual patients. The reliability of the pimple sign is reassuring, but not surprising, given the reliability with which non-experts could classify patients based on statistical metabolic maps as mentioned above. Our findings suggest that a 'definite' pimple sign can add to existing metabolic abnormalities defining PSPS and assist in identifying individual patients as likely having PSPS.

A major strength of the current study is the large number of PSPS and CBS patients. Prior projects have focussed primarily on differentiating PD from atypical parkinsonian disorders, or differentiating PSPS from controls, and there is a relative shortage of work on differentiating between PSPS and CBS, especially considering the variable phenotypes of CBS and the high rate of misdiagnosis [16]. By comparing corrected midbrain volumes among patients with and without the pimple sign we were also able to better define the anatomic abnormalities underlying apparent hypometabolism. Our study has several limitations, however, most notably the shortage of MSA patients, particularly MSA-P patients. This is primarily because these patients often don't proceed to have FDG-PET imaging done, with the diagnosis established on the basis of other investigations. Similarly, since PSPS can mimic behavioral variant frontotemporal dementia, including patients with this diagnosis would further add to the clinical utility of the sign. FDG-PET scans in our study were normalized to the pons, which is the

standard area of normalization we use in our clinical practice. The pons has, however, been implicated in some patients with MSA and PSP [33], and it might have been advantageous to use global metabolism as a means to normalize the scan. Since any pontine hypometabolism would result in a relative decrease in the observed midbrain hypometabolism, there is a possibility that some of the 'possible' cases might have more clearly demonstrated the pimple sign if we had normalized the scans to global metabolism, which would alter the sensitivity and specificity of the sign, though this is not guaranteed. Overall, we do not feel this significantly affected our results.

A further limitation of our project, and most previous FDG-PET studies on PSPS, stems from the fact that the clinical diagnosis at the time of PET is often used as gold standard. For PET imaging to be incorporated into the diagnostic evaluation it would have to be shown to result in an improvement on the sensitivity and/or specificity of the clinical evaluation. Pathological data on all 11 patients that expired would have been ideal, but given the remarkably high specificity of the NINDS-SPSP criteria for both possible (93–99%) and probable (near perfect) PSP, the lack of pathological confirmation is not necessarily a major limitation [16]. Future work could assess the presence of the pimple sign in patients who do not meet diagnostic criteria for a specific disorder and then follow these patients longitudinally to determine whether the pimple sign is predictive of a diagnosis of PSP.

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Conflicts of interests

The authors declare that they have no conflict of interest.

Author roles

Research project:
A. Conception: KAJ, JLW.
B. Organization: HB, KAJ, JLW.
C. Execution: HB, KAJ, JLW, AM, MLS, VL.
Statistical Analysis:
A. Design: HB, KAJ.
B. Execution: HB.
C. Review and critique: KAJ, JLW.
Manuscript Preparation:
A. Writing of the first draft: HB.
B. Review and critique: KAJ, JLW, VL, AM, MLS.
C. Finalizing the manuscript: HB, KJ.

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