

Reference Standard

All patients underwent standard work-up including cranial and spinal MR imaging ($n = 40$), MR myelography ($n = 28$), digital subtraction myelography with subsequent CT myelography (DSM/CTM) ($n = 40$) and dynamic CSF testing using a computerized lumbar constant infusion ($n = 36$). Of note, numerous patients underwent repeated examination, which is of particular interest in case of DSM/CTM because of the high radiation exposure ($n = 15, 13, 10$ and 2 patients underwent $1, 2, 3$ and 4 DSM/CTM, respectively). All findings were presented to an interdisciplinary SIH Board including experienced physicians from the Departments of Neurosurgery, Neurology and Neuroradiology, who discussed each case and diagnosis and suggested the appropriate treatment.

⁶⁸Ga-DOTA

The preparation of ⁶⁸Ga-DOTA was performed in a clean room using fully automated GMP-compliant synthesis module (Modular-Lab PharmTracer, Eckert & Ziegler) with low bioburden single-use cassettes (supplied by Eckert & Ziegler, EUROTOPE GmbH). Isotonic saline, sodium hydrogen phosphate solution pH 7 (solution for infusion, Braun®) and ⁶⁸Ge/⁶⁸Ga generator (Eckert & Ziegler, EUROTOPE GmbH) were connected to the cassette. The reaction vessel was preloaded with 99 nmol 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) in $470 \text{ }\mu\text{L}$ sodium acetate buffer (pH 4.5). [⁶⁸Ga]GaCl₃ (860 MBq) was pre-concentrated on strong cation exchange cartridge and eluted with NaCl/HCl into reaction vessel and the radiosynthesis was carried out at $95 \text{ }^{\circ}\text{C}$ for 500 seconds . The resulting solution was cooled down, diluted with isotonic saline, neutralized with sodium hydrogen phosphate solution (pH 7) and passed through a $0.22 \text{ }\mu\text{m}$ sterile membrane filter into a capped sterile vial. Subsequently, aliquots were taken for quality control (QC) and sterility tests. The QC process was performed in adherence to European Pharmacopeia standards and according to standard operating procedures including filter integrity, pH test, limulus amebocyte lysate (LAL), radionuclide identity and purity test by determining half-life and energy spectrum. Radiochemical purity ($\geq 98 \text{ }\%$) was identified by radio-TLC. The sterility

tests were conducted by an independent institution (Biochem GmbH, Karlsruhe) according to Ph. Eur. and USP using direct inoculation method.

PET Acquisition

All PET scans were acquired on a fully digital PET/CT system (Vereos, Philips Healthcare, The Netherlands) at 1, 3 and 5 hours after lumbar intrathecal injection of ^{68}Ga -DOTA (about 45-50 MBq in 0.5-1.0 ml volume) under strictly sterile conditions (usually, an atraumatic 21 G spinal needle was used) in a sitting position aiming at the lumbar levels 3/4. After injection, patients were asked to remain in their beds until scanning in supine position and not to void their bladders until the 1-h scan was completed (return to bed afterwards). From the decay-corrected total radioactivity within the whole-body scan at 1 h, the net intrathecally injected dose was estimated to be 38.1 ± 10.2 MBq.

PET/CT scans were acquired in caudocranial direction covering the body from bladder to head (except in one patient in whom the scan was confined to the base of the skull). Scan time was 2.0 min (1-h and 3-h scan) and 3.0 min (5-h scan) per bed position (16.4 cm) with an overlap of 39%. Ultra-lose-dose (100 kV and 15 mAs) and lose-dose (120 kV and 23 mAs) CT scans for attenuation correction and anatomical correlation were acquired at 1 and 5 h, and 3 h, respectively. Care was taken to re-position the patients as good as possible to allow for a co-registration of all three datasets (i.e., strictly aligned to the bed axis, arms held up, same head and knee rests, etc.). Fully corrected PET datasets were reconstructed employing the vendor-specific, line-of-response, time-of-flight, ordered-subsets, 3-dimensional iterative reconstruction algorithm using spherically symmetric basis functions (so-called blob ordered subset time-of-flight reconstruction; number of iterations, 3; number of subsets, 9; no gaussian postfiltering; resulting voxel size, 2.0 x 2.0 x 2.0 mm; resolution recovery with point spread function: number of iterations, 2; regularization kernel: 6 mm).

Because of clinical or logistics needs the actual start times of PET scans may slightly deviate from the planned scan times (59.8 ± 7.1 min, 183.1 ± 4.7 min and 305.9 ± 13.8 min, respectively; relevant deviations occurred in 3 scans in one patient each, who were scanned at 30 and 35 min instead of 1 h and

375 min instead of 5 h). For reasons of simplicity, we will nevertheless refer to the consecutive scans as 1-h, 3-h and 5-h scans.

Visual PET Reads

Two Nuclear Medicine physicians with long-lasting experience in neuroimaging, who were blinded to all other clinical and diagnostic data as well as the results of quantitative PET analyses (see below), re-evaluated all ^{68}Ga -DOTA-PET scans independently. Using maximum intensity projections (individually scaled for optimal display) and cross-sectional images (uniform display: inverted grey scale, SUV minimum and maximum fixed to 0 and 40 g/ml) of the 1-h, 3-h and 5-h PET/CT datasets, visual reads of direct and indirect RC signs and a summary rating were done as follows:

Directs signs of spinal CSF leak include uni- or bilateral paraspinal, extradural tracer accumulation, which was localized according to 28 spinal segments (defined by 24 vertebral bodies including the caudal adjacent intervertebral space plus 1 suboccipital and 3 sacral segments) and graded in 3 steps (0, none; 1, questionable/mild signal; 2, strong signal) at each time point. To be counted as a positive site of tracer egression, this had to be witnessed at least at one time point. In case of extradural tracer accumulation on multiple consecutive segments, these were rated in combination (assuming that they stem from the same process and to reduce the data). Of note, findings were carefully separated from prominent dural sleeves (in particular, lumbar), intact meningeal diverticula and Tarlov cysts.

Indirect signs of spinal CSF leak include radiotracer accumulation in the bladder (1-h scan only) and radiotracer accumulation in the basal cisterna and over the cerebral convexities. Again, a 3-step scale was employed (see above). As very low tracer accumulation in the neurocranium can hardly be differentiated from scattered photons, the signal level of the arms (i.e., scattered activity; positioned next to the head) was used as threshold. In addition, the raters assessed iatrogenic tracer extravasation at the injection site confined to the trajectory of the needle (rated in 3 steps).

Finally, a 3-step summary rating was recorded by each rater for each individual case considering all aforementioned findings (i.e., 0, 1 and 2 for no, questionable/possible and probable CSF leakage, respectively, including the segment, if identified).

After both raters performed independent ratings in separate sessions, they discussed discrepant cases and reached a consensus on the localization of CSF egression (if differing by more than 1 segment) and the summary rating. We calculated the mean score of both raters for all other ratings (i.e., magnitude of indirect signs and tracer accumulation).

Quantitative PET Analysis

The time course of total radioactivity within the CSF space was characterized in terms of biological half-life ($T_{1/2, \text{biol}}$) and, as a simplified approach, using the ratio of total radioactivity within the CSF space at 5 h and 3 h (referred to as R5/3; using data decay-corrected to the time of injection). Analyses were performed as follows using PMOD (Version 3.7; PMOD Technologies LLC, Switzerland):

First, the individual 1-h and 5-h PET scans were automatically co-registered to the patient's 3-h scan (rigid matching with a normalized mutual information algorithm as implemented in PMOD). Then individual whole-body and CSF-space volumes of interest (VOI) were defined as rectangular regions covering the entire dataset (VOI_{wb}) and CSF space (VOI_{CSF} ; from head to sacral region, carefully excluding extradural activity due to leakage and, for instance, urinary excretion), respectively. These VOI were applied to all individual datasets (and possibly manually corrected if not sufficiently fitting the 1-h and 5-h dataset) to assess decay-corrected total radioactivity within each VOI and time point. Since patients were asked not to void their bladder before the 1-h scan, decay-corrected total radioactivity in the 1-h scan can be assumed to reflect the total amount of ^{68}Ga -DOTA injected into the CSF space (see above). Finally, the decay-corrected total radioactivity within VOI_{CSF} in the 1-h, 3-h and 5-h scans was used to estimate $T_{1/2, \text{biol}}$ by a mono-exponential fit (using actual scan times; see small variations in scan time mentioned above), while R5/3 was calculated directly from total radioactivity within the 3-h and 5-h scans (we also linearly extrapolated R5/3 from actual scan times, but given the small variations this had no relevant effect on overall

results). We did not include the net injected dose (i.e., VOI_{CSF} at 0 h) into the fit of $T_{1/2,\text{biol}}$ because the radiopharmaceutical needs some time to distribute along the dural space in caudocephal direction and to reach the putative site of leakage. In turn, at 1 hour after injection, the radiotracer usually covers the entire spinal axis (see Results), allowing us to approximate $T_{1/2,\text{biol}}$ by a simple mono-exponential fit.

Statistical Analysis

Correlations between continuous and ordinal variables were assessed by Pearson's r (parametric) and Spearman's ρ (non-parametric) correlation coefficients, as appropriate. We checked for a dependency of visual ratings (direct and indirect signs, averaged across raters) on scan time, presence/absence of spinal CSF leakage and their interaction by analysis of covariance including subject ID as random effect. The association between epidemiological variables, qualitative and quantitative PET analyses and the presence or absence of a spinal CSF leak (see reference standard) was investigated by two-sample t test (continuous data) or Wilcoxon test (Mann-Whitney U test; ordinal data). Given the novelty of the presented methodology and the exploratory nature of the present study, we employed no correction for multiple testing. However, we drastically reduced the number of variables by averaging over raters, sites and time points. In case of significant findings, a receiver operating characteristics (ROC) analysis was performed to assess the diagnostic performance of the respective PET parameter by the area under the ROC curve (AUC_{ROC}). The optimal diagnostic cut-off point was defined by the maximum Youden's index. Finally, in an exploratory analysis we used stepwise forward regression with minimum corrected Akaike Information Criterion (AIC) to choose the best model for prediction of spinal CSF leakage. All analyses were done with JMP (Version 11.0.0, SAS Institute Inc., USA).

METHODS

Visual PET Reads – Inter-rater Agreement

Visual reads of direct signs of a spinal CSF leak were highly consistent between both raters: Both investigators rated 11 patients each to show no direct evidence of tracer egression. In 10 cases the rating

was unanimously. In one case each, the other rater missed one and two sites of tracer egression, respectively, according to their final consensus. In the remaining 27 patients both raters agreed that the patients showed at least one direct sign of tracer egression. Their rating was unanimously positive for 46 sites and differed either in location by more than 1 segment or presence of tracer egression in 7 sites. Taken together, the raters agreed in 56/66 (86%) of ratings.

Ratings of indirect signs of CSF leakage and tracer extravasation at the injection site were also highly consistent between observers: Concerning the rating of radiotracer accumulation in the bladder (1-h scan only), in the basal cisterna and over the cerebral convexities (n = 1 patient's head not within the field of view) both raters agreed in 33/39 (85%), 91/114 (80%) and 95/114 (83%) of ratings and only rarely differed by more than one point (one basal cisterna and cerebral convexity rating each). The same is true for the rating of the tracer extravasation at the injection site (99/117 [85%]).

Both raters also filed a summary score considering all direct and indirect signs. These ratings were highly consistent (complete agreement in 30/39 [77%] of ratings, differing by 2 in only one case). Both observers' ratings showed highly significant groups differences with rater 1 yielding a slightly higher diagnostic performance for separation of patients without and with verified spinal CSF leak (rater 1: 0.52 ± 0.68 vs. 1.52 ± 0.72 , $p = 0.0003$, AUC ROC = 0.82; rater 2: 0.38 ± 0.67 vs. 1.28 ± 0.89 , $p = 0.0022$, AUC ROC = 0.76).

Time course of direct and indirect RC signs

Sites of extrathecal tracer accumulation at the craniocervical junction were more pronounced at later time points; however, this failed to reach statistical significance given the small number (n=3; 1-h, 3-h and 5-h scan: 0.50 ± 0.50 , 1.67 ± 0.58 and 1.33 ± 0.58 , respectively). Findings at the cervicothoracic junction showed no dependency on time (n=14; 1-h, 3-h and 5-h scan: 0.96 ± 0.77 , 1.11 ± 0.59 and 0.82 ± 0.64), whereas those in the lower thoracic spine ($p=0.0081$; n=12: 1.54 ± 0.58 , 1.21 ± 0.66 and 0.88 ± 0.83 , respectively) and in the lumbosacral region ($p=0.019$; n=22: 1.50 ± 0.67 , 1.43 ± 0.58 and 1.05 ± 0.69 , respectively) showed a

significant decrease with time. Presence/absence of a spinal CSF leak and its interaction with time had no significant effect on the time course in any region.

Ratings of the basal cisterna showed a significant increase with time ($p<0.0001$; 1-h, 3-h and 5-h scan: 1.41 ± 0.64 , 1.79 ± 0.46 and 1.76 ± 0.46 , respectively) and interaction with the presence/absence of a spinal CSF leak ($p=0.049$; significant increase with time only in those without CSF leakage). The tracer accumulation over the cerebral hemispheres was highly dependent on time ($p<0.0001$; 1-h, 3-h and 5-h scan: 0.03 ± 0.11 , 0.62 ± 0.54 and 1.01 ± 0.85 , respectively), presence/absence of a spinal CSF leak ($p=0.0082$; 0.34 ± 0.51 vs. 0.72 ± 0.80 , across all time points) and their interaction ($p<0.0001$; significantly steeper increase with time in those without CSF leakage) (Figure 1-4). Finally, the ratings of tracer extravasation at the injection site showed a significant negative association with scan time only ($p=0.0023$; 1-h, 3-h and 5-h scan: 0.68 ± 0.82 , 0.58 ± 0.75 and 0.44 ± 0.63 , respectively).

Supplemental Table 1: Results of Visual and Quantitative PET Analyses (patients with SIH without previous surgery or alternative causes)

| Parameter | | w/o leak (n=13) | w/ leak (n=18) | <i>p</i> | <i>ROC AUC</i> |
|-------------------------|---------------------------|-----------------|----------------|----------|----------------|
| Bladder activity | 1 h | 1.31±0.66 | 1.42±0.55 | n.s. | - |
| Basal cisterna | 1 h | 1.08±0.64 | 1.53±0.62 | n.s. | - |
| | 3 h | 1.77±0.44 | 1.74±0.56 | n.s. | - |
| | 5 h | 1.69±0.43 | 1.71±0.56 | n.s. | - |
| Cerebral convexities | 1 h | 0.00±0.00 | 0.03±0.12 | n.s. | - |
| | 3 h | 0.54±0.48 | 0.50±0.59 | n.s. | - |
| | 5 h | 1.15±0.92 | 0.50±0.56 | 0.0360 | 0.69 |
| Craniocervical (SO-C1) | | 0.00±0.00 | 0.19±0.47 | (0.0987) | (0.58) |
| Cervicothoracic (C6-T2) | | 0.10±0.25 | 0.68±0.58 | 0.0010 | 0.79 |
| Lower thoracic (T7-T12) | | 0.45±0.75 | 0.44±0.64 | n.s. | - |
| Lumbosacral (L2-S2) | | 0.77±0.82 | 0.79±0.81 | n.s. | - |
| Consensus summary read | | 0.54±0.78 | 1.39±0.78 | 0.0058 | 0.77 |
| PET quantification | T _{1/2,biol} [h] | 8.8±5.93 | 4.54±2.45 | 0.0345 | 0.69 |
| | R5/3 | 0.78±0.18 | 0.63±0.18 | 0.0319 | 0.74 |

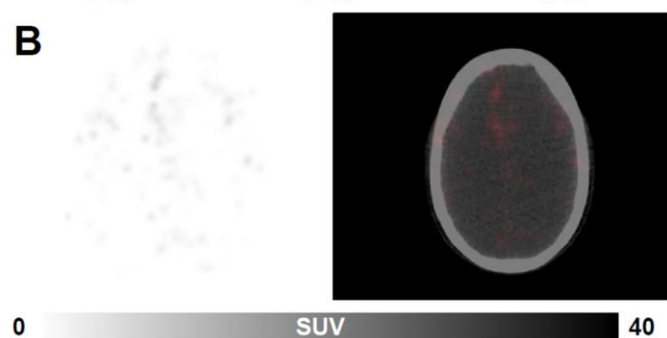
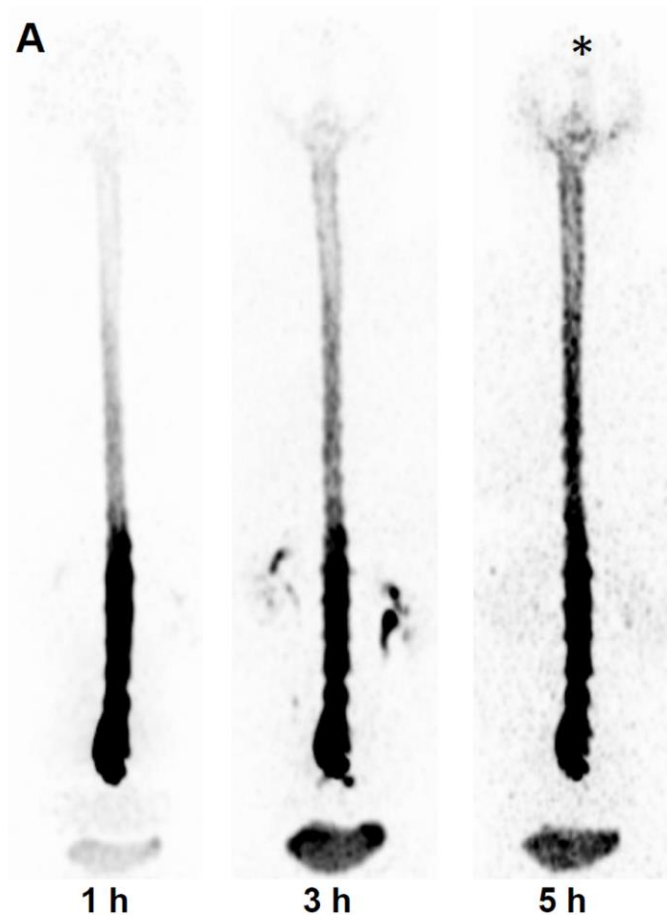
Except for PET quantification, all data represent 3-step ordinal scales with values giving mean values across readers and times (if not separated) or the consensus of raters. Given are mean values ± standard deviation, *p* values of statistical comparisons between patients without (w/o) and with (w/) spinal CSF leak (n.s., not significant, *p* values in parenthesis indicate trend effects) and area under the receiver operating characteristics curve (*ROC AUC*; only for significant and trend effects). Anatomical localizations refer to sites of tracer accumulation (spinal segments; SO, suboccipital). SIH, spontaneous intracranial hypotension.

| No. | Leak | Injection Site | | | Bladder 1h | Basal | | Cisterna 1h 3h 5h | Convexities | | | Cervical | | | | | | | Thoracic | | | | | | | | | | | | Lumbar | | | | | Sacral | | | Consensus Summary | PET Quantification | | | |
|-----|------|----------------|-----|-----|---------------|-------|-----|----------------------|-------------|-----|-----|----------|-----|----|----|----|----|-----|----------|----|----|----|----|-----|----|----|----|----|----|-----|--------|-----|----|----|----|--------|----|----|----------------------|--------------------|-------|---------------|------|
| | | 1h | 3h | 5h | | 1h | 3h | | 5h | 1h | 3h | 5h | S0 | C1 | C2 | C3 | C4 | C5 | C6 | C7 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 | L1 | L2 | L3 | L4 | L5 | S1 | | S2 | S3 | T1/2,biol [h] | R5/3 |
| 14 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 2 | 0 | 1.5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 28.27 | 0.98 | | |
| 9 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 14.76 | 0.96 | | |
| 23 | 0 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13.78 | 0.90 | | |
| 37 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13.75 | 0.96 | | |
| 20 | 0 | 0 | 1 | 1 | 0.5 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 13.06 | 0.83 | | |
| 7 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12.76 | 0.96 | | |
| 15 | 0 | 2 | 1.5 | 1 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10.07 | 0.85 | | |
| 40 | 0 | 0.5 | 1 | 0.5 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9.63 | 0.85 | | |
| 21 | 0 | 0.5 | 0 | 0 | 1.5 | 2 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9.02 | 0.86 | | |
| 1 | 0 | 0 | 0 | 0 | 2 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5.96 | 0.80 | | |
| 38 | 0 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4.92 | 0.83 | |
| 24 | 0 | 0.5 | 0.5 | 0 | 2 | 2 | 2 | 1.5 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2.53 | 0.50 | | |
| 35 | 0 | 2 | 2 | 1.5 | 0.5 | 1.5 | 2 | 2 | 0.5 | 1.5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 31 | 0 | 2 | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 0.5 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 28 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0.7 | 0.7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 20.76 | 0.94 | |
| 5 | 0 | 2 | 2 | 1.5 | 2 | 2 | 2 | 2 | 0 | 0.5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2.73 | 0.72 | |
| 26 | 0 | 1.5 | 1 | 1.5 | 2 | 2 | 2 | 2 | 0 | 0.5 | 1.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2.67 | 0.65 | |
| 29 | 0 | 0 | 0 | 0 | 1 | 1 | 1.5 | 2 | 0 | 0.5 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2.67 | 0.63 | |
| 8 | 0 | 2 | 2 | 1 | 1.5 | 1 | 2 | 1.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1.53 | 0.45 | |
| 3 | 0 | 0 | 0 | 0 | 0.5 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 7.51 | 0.78 | |
| 6 | 0 | 2 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3.61 | 0.66 | |
| 36 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10.64 | 0.86 | |
| 11 | 1 | 0 | 0 | 0 | 1 | 2 | 2 | 2 | 0 | 0.5 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7.23 | 0.78 | |
| 19 | 1 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 0.5 | 1 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6.06 | 0.80 | |
| 30 | 1 | 1 | 1 | 0.5 | 1 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4.80 | 0.63 | |
| 4 | 1 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4.02 | 0.63 | |
| 18 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3.01 | 0.51 | |
| 2 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2.66 | 0.60 | |
| 33 | 1 | 1.5 | 0.5 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0.45 | 0.09 | |
| 25 | 1 | 0 | 0 | 0 | 1 | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 7.86 | 0.82 | |
| 34 | 1 | 0 | 0 | 0 | 1 | 1 | 2 | 1.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 6.09 | 0.75 | |
| 17 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 2 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 5.66 | 0.74 |
| 27 | 1 | 0 | 0 | 0 | 2 | 1 | 1.5 | 1.5 | 0 | 0 | 0 | 0.7 | 0.7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 5.52 | 0.72 |
| 22 | 1 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3.65 | 0.63 | |
| 32 | 1 | 0 | 0 | 0 | 0.5 | 2 | 2 | 2 | 0 | 0.5 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3.45 | 0.59 | |
| 12 | 1 | 1.5 | 0.5 | 0 | 2 | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3.34 | 0.62 | |
| 16 | 1 | 0 | 0 | 0 | 1 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 1.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2.72 | 0.46 | |
| 10 | 1 | 0 | 0 | 0 | 2 | 2 | 2 | 2 | 0 | 0.5 | 0.5 | 1.3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2.66 | 0.56 | |
| 39 | 1 | 0.5 | 0.5 | 0.5 | 2 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1.97 | 0.51 | |

Supplemental Figure 1: Heatmap of CSF-PET findings in patients without (n=21) and with (n=18) verified spinal CSF leak.

Color coding refers to the degree of abnormality (green, normal to red, abnormal). Data is sorted by (i) absence or presence of verified spinal CSF leak (thick horizontal line; segmental height of verified leak is indicated by a thick box), (ii) consensus of visual summary read (Consensus Summary; thin horizontal line) and (iii) biological half-life of the tracer in CSF space (T_{1/2,biol}).

Except for absence or presence of a spinal CSF leak (Leak; binary scale) and PET Quantification (T_{1/2,biol} and R5/3; continuous data), all data represent 3-step ordinal scales with values giving mean values across readers and times (if not separated) or the consensus between both raters. Anatomical localizations refer to the sites of tracer accumulation (Convexities, activity over cerebral convexities).



Supplemental Figure 2: Pathological CSF-PET in a patient without verified spinal CSF leak but response to epidural blood patch.

A, maximum intensity projections of PET at 1h, 3h and 5h (posterior view; scaled for optimal display) after injection of ^{68}Ga -DOTA. B, transaxial PET and PET/CT fusion images at the level of the centrum semiovale (5h). Despite that no spinal CSF leak could be verified by comprehensive stepwise neuroradiological work-up, there is an apparent lack of tracer accumulation over the cerebral convexities (asterisk). In addition, the biological half-life of the tracer in the CSF space was very short (2.7 h). The patient (No. 29) was treated by epidural blood patch with improvement of symptoms.