nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data collection used clinical MRI acquisition, whole-slide imaging, laboratory assays, and sequencing platforms as described in the Methods. Whole-slide images were acquired using a Leica Aperio AT2 scanner and visualised or assessed using Aperio ImageScope software v12.4.6.50003. QuPath v0.6.0 was used for annotation and image-based analyses of ISH-stained whole-slide images. Supervised pixel classifiers were trained using QuPath's built-in "Train pixel classifier" functionality and then applied uniformly to annotated regions of interest for quantitative analysis. StarDist2D pretrained models for QuPath were used for cell detection where applicable and are publicly available through the QuPath model repository. MRI segmentation used FreeSurfer v7.3.2/SynthSeg and multi-atlas label-fusion methods. mNGS libraries were sequenced on a NextSeq1000 platform.
Data analysis	Publicly available software used in the study included QuPath v0.6.0, Aperio ImageScope v12.4.6.50003, Python 3.11, FreeSurfer v7.3.2/ SynthSeg, SPAdes v3.15.3, BLASTn v2.12.0, Bowtie2 v2.2.5, Samtools v1.15.1, Picard v2.23.0, and Bamtools v2.5.2. Data analysis used Microsoft Excel, GraphPad Prism v10.4.2, QuPath v0.6.0, Python 3.11, and Aperio ImageScope v12.4.6.50003. Viral sequence analyses used SPAdes v3.15.3, BLASTn v2.12.0, Bowtie2 v2.2.5, Samtools v1.15.1, Picard v2.23.0, and Bamtools v2.5.2. GraphPad Prism was used for non-parametric tests, correlations, regression analyses, heatmaps, and graphs. Custom scripts were used for selected image quantification and derived indices and are available from the corresponding author upon reasonable request.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All data are available from the corresponding author upon reasonable request. Whole-slide image files and clinical data are not deposited publicly because they derive from a single fatal human case and may contain potentially identifiable information.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	This is a single-patient case report. Sex was obtained from the medical record, confirmed during autopsy examination, and reported descriptively as female. Sex was not used as a study design variable, and no sex-based comparative analyses were performed.
Reporting on race, ethnicity, or other socially relevant groupings	Not applicable. This manuscript describes a single fatal case and does not use race, ethnicity, or other socially relevant groupings as analytical variables. No comparisons or inferences are made on the basis of these categories.
Population characteristics	This is a single-patient case report, and no covariate-based population analyses were performed. Relevant patient characteristics are reported descriptively, including age, sex, past and current diagnoses, therapies, clinical presentation, diagnostic findings, and postmortem CNS tissue findings.
Recruitment	This is a single-patient case report; no participant recruitment was performed. Postmortem tissue specimens from an individual with Potosi virus (POTV) infection and fatal neurologic disease were submitted to CDC's Infectious Diseases Pathology Branch on June 2025 for pathology consultation and diagnostic evaluation. Available medical and autopsy records submitted as part of the diagnostic consultation were reviewed.
Ethics oversight	This activity was reviewed by CDC and determined not to constitute human-subjects research under 45 CFR 46 because it involved postmortem tissues and clinical information from a deceased individual. Research involving deceased individuals is not human subjects research according to 45 CFR 46.102(e1) and does not require IRB oversight. The next of kin provided written consent for autopsy examination, this study, and publication of the study findings. The investigation was conducted as part of a public health investigation and consistent with applicable federal law and CDC policy, including 45 CFR part 46, 21 CFR part 56, 42 USC §241(d), 5 USC §552a, and 44 USC §3501 et seq.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	This is a single-patient case report. No sample-size calculation was performed because the study describes one fatal case of a CNS infection evaluated through diagnostic consultation, postmortem examination, and tissue-based analyses.
Data exclusions	No patient-level data were excluded. Analyses were performed on available clinical, neuroimaging, laboratory, and postmortem tissue data. Individual tissue regions or assays were included when adequate tissue, image quality, or sequencing data were available for the specified analysis.
Replication	Formal replication in an independent cohort was not applicable because this is a single-patient case report of a rare, newly recognised infection. Findings were assessed using complementary approaches, including histopathology, IHC, ISH, RT–PCR, mNGS, longitudinal MRI, and quantitative image-based analyses.
Randomization	Randomization was not applicable. This was a single-patient observational case report, and no participants, samples, or organisms were allocated to experimental groups.
Blinding	Blinding to group allocation was not applicable because there were no experimental groups. Quantitative image-based analyses were applied to predefined regions of interest using standardised approaches; pathology findings were interpreted in the context of diagnostic and postmortem evaluation.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
[ ]	[x] Antibodies
[x]	[ ] Eukaryotic cell lines
[x]	[ ] Palaeontology and archaeology
[x]	[ ] Animals and other organisms
[ ]	[x] Clinical data
[x]	[ ] Dual use research of concern
[x]	[ ] Plants

Methods

n/a	Involved in the study
[x]	[ ] ChIP-seq
[x]	[ ] Flow cytometry
[ ]	[x] MRI-based neuroimaging

Antibodies

Antibodies used	Primary antibodies used for immunohistochemistry included a mouse monoclonal anti-Cache Valley virus/orthobunyavirus nucleoprotein antibody for POTV antigen detection, anti-Escherichia coli, anti-prion protein, CD20, Iba1, and NeuN. Supplier, clone, dilution, pretreatment, and source information are provided in the Methods and Supplementary Table 21.
Validation	Antibodies were selected on the basis of established diagnostic use, manufacturer documentation, published validation, and/or in-house assay validation for formalin-fixed paraffin-embedded tissues. The anti-Cache Valley virus/orthobunyavirus nucleoprotein antibody was previously validated in-house, and it was shown to cross-react with multiple orthobunyaviruses, including Potosi virus. Appropriate positive and negative controls were run in parallel for each antibody. Validation details and antibody pretreatments are provided in the Methods and Supplementary Table 21.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Not applicable. This is a single-patient case report and not a clinical trial.
Study protocol	Not applicable. This is a single-patient case report based on diagnostic consultation, postmortem examination, and available clinical records; no prospective clinical study protocol was used.
Data collection	Clinical data were obtained from available medical and autopsy records submitted as part of the diagnostic consultation. Postmortem tissue specimens were submitted to CDC's Infectious Diseases Pathology Branch for pathology consultation and diagnostic evaluation.
Outcomes	Not applicable. No prespecified clinical trial outcomes were defined. This is a single-patient case report and not a clinical trial.

Plants

Seed stocks	Not applicable
Novel plant genotypes	Not applicable
Authentication	Not applicable

Magnetic resonance imaging

Experimental design

Design type	No fMRI

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s): structural

Field strength: 1.5 and 3

Sequence & imaging parameters: sequence type: spin echo, field of view: 200x220mm, matrix: 228x256, slice thickness: 4mm, orientation: axial, echo time: 17msec, repetition time: 608msec, flip angle: 90 degrees
sequence type: 3D gradient echo, field of view: 176x240mm matrix size: 176x240, voxel dimension: 1mm, orientation: sagittal, echo time: 2.03msec, repetition time: 2300msec, inversion time: 900msec, flip angle: 9 degrees

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: N3 v1.12.00, FreeSurfer v7.3.2

Normalization: None

Normalization template: None

Noise and artifact removal: None

Volume censoring: None

Statistical modeling & inference

Model type and settings: Not available

Effect(s) tested: Not available

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☒ Both

Anatomical location(s): Cerebellar gray matter, cerebellar white matter, caudate, hippocampus, thalamus, putamen, cerebral cortical gray matter, cerebral white matter

Statistic type for inference (See Eklund et al. 2016): Not available

Correction: Not available

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis