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Evaluation of a Non-Human Primate Model Using Cisterna Magna CSF Cannulation for Intracisternal Drug Delivery and Repeated Cerebrospinal Fluid Sampling

大槽内CSFカニュレーションモデルを用いた大槽脊髄内薬物送達および髄液反復採取のための非ヒト霊長類モデルの検討

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Summary in Japanese

本研究では、覚醒下でCSFの反復採取が可能なカニクイザル大槽内カテーテル留置モデルを構築した。

- CSF試料の品質はTP、ALBおよびRBC測定により確認し、TPおよびALBは正常範囲内であり、RBCは検出されなかった。
- Aβ40、Aβ42、Aβ42/40比、α-シヌクレイン、p-TauおよびNfLを含むCSFバイオマーカーには、明確な日内変動は認められなかった。
- パクリタキセル投与後1および2週間でNfLの上昇が認められ、神経毒性バイオマーカーとしての有用性が示された。
- 腰部髄腔内に投与したEvans Blueは大槽CSF中で検出され、頭側移行が確認された。

以上より、本モデルは、CSFバイオマーカーの縦断解析、神経毒性評価、および髄腔内投与後の頭側分布評価に有用な非臨床評価基盤であると考えられた。

Objective

To establish a cisterna magna catheterization model in cynomolgus monkeys that enables repeated CSF collection under conscious conditions, and to evaluate its applicability as a nonclinical CNS assessment platform for the development of therapeutics for neurodegenerative diseases. Using this model, we aimed to assess longitudinal changes in CSF biomarkers including Aβ40, Aβ42, Aβ42/40 ratio, α-synuclein, p-Tau, and NfL, confirm CSF sample quality by TP, ALB, and RBC measurements, evaluate rostral distribution after lumbar intrathecal administration using Evans Blue, and examine the utility of NfL as a neurotoxicity biomarker after paclitaxel administration.

Materials and Methods

Animal/Cannulation

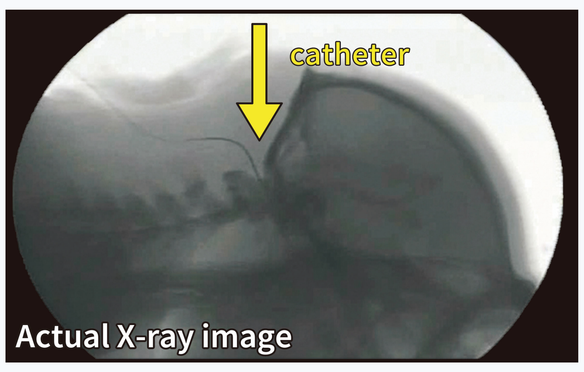
Four cynomolgus monkeys, No. 102 (male), No. 201, No. 202, and No. 203 (females), aged 9–10 years, were used. A catheter was implanted into the cisterna magna, and a subcutaneous access port was placed in the cervicodorsal region.

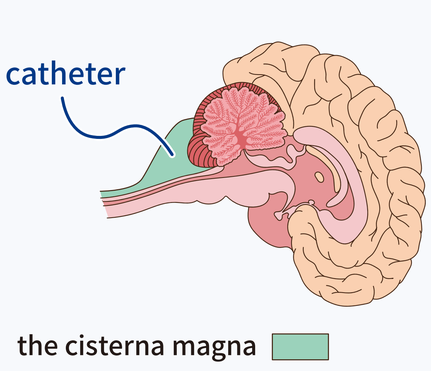
CSF sampling

Approximately 250 µL of CSF was collected at each sampling point under conscious conditions. After centrifugation at 18000×g for 1 min at 4°C, the supernatant was used for biomarker and biochemical analyses, and the pellet was used for RBC assessment.

Evaluation items

1) CSF biomarkers: Aβ40, Aβ42, Aβ42/40 ratio, α-Syn, p-Tau, and NfL
2) CSF quality: TP, ALB, and RBC
3) Evans Blue: Absorbance at 620 nm in cisterna magna CSF after IT administration at L5–6
4) Paclitaxel: Administered as a positive control for neurotoxic changes; NfL levels were evaluated at 1 and 2 weeks after administration.





Conclusion

- A cisterna magna cannulation model enabling repeated CSF collection under conscious conditions was established.
- TP and ALB were within reference ranges, and RBC was 0 cells/µL, indicating good CSF quality without blood contamination.
- Major CSF biomarkers showed no notable diurnal variation, providing stable baseline data for interpreting drug-induced changes.
- CSF NfL was higher than previously reported values in No. 201 and No. 203, both evaluated 1 month after cannulation surgery, suggesting that this interval may be too short for NfL-based assessment.
- NfL increased at 1 and 2 weeks after paclitaxel administration, supporting its utility as a biomarker reflecting axonal injury.
- Evans Blue detection in cisterna magna CSF enabled direct evaluation of rostral distribution after lumbar IT administration.
- This system may be useful for CNS safety assessment and neurotoxicity biomarker evaluation.

Results

1 CSF Quality: Assessment of Albumin Levels and Sample Quality in CSF

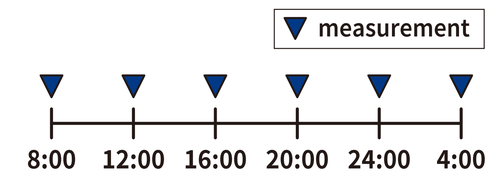
Parameter	Literature reference value	Animal ID	Measured value
TP	< 200 mg/dL	No. 102 No. 202	43 mg/dL 55 mg/dL
ALB	10–40 mg/L	No. 102 No. 202	20.9 mg/L 22.1 mg/L
RBC	0 cells/µL (normal CSF)	No. 102 No. 202	0 0

TP and ALB levels in cynomolgus monkey CSF were within the reference ranges reported in the literature.
In addition, RBCs were not detected, indicating no apparent blood contamination.

Representative data from No. 102 and No. 202 are shown.

2 Diurnal Variation of CSF Biomarkers

Experiment schedule

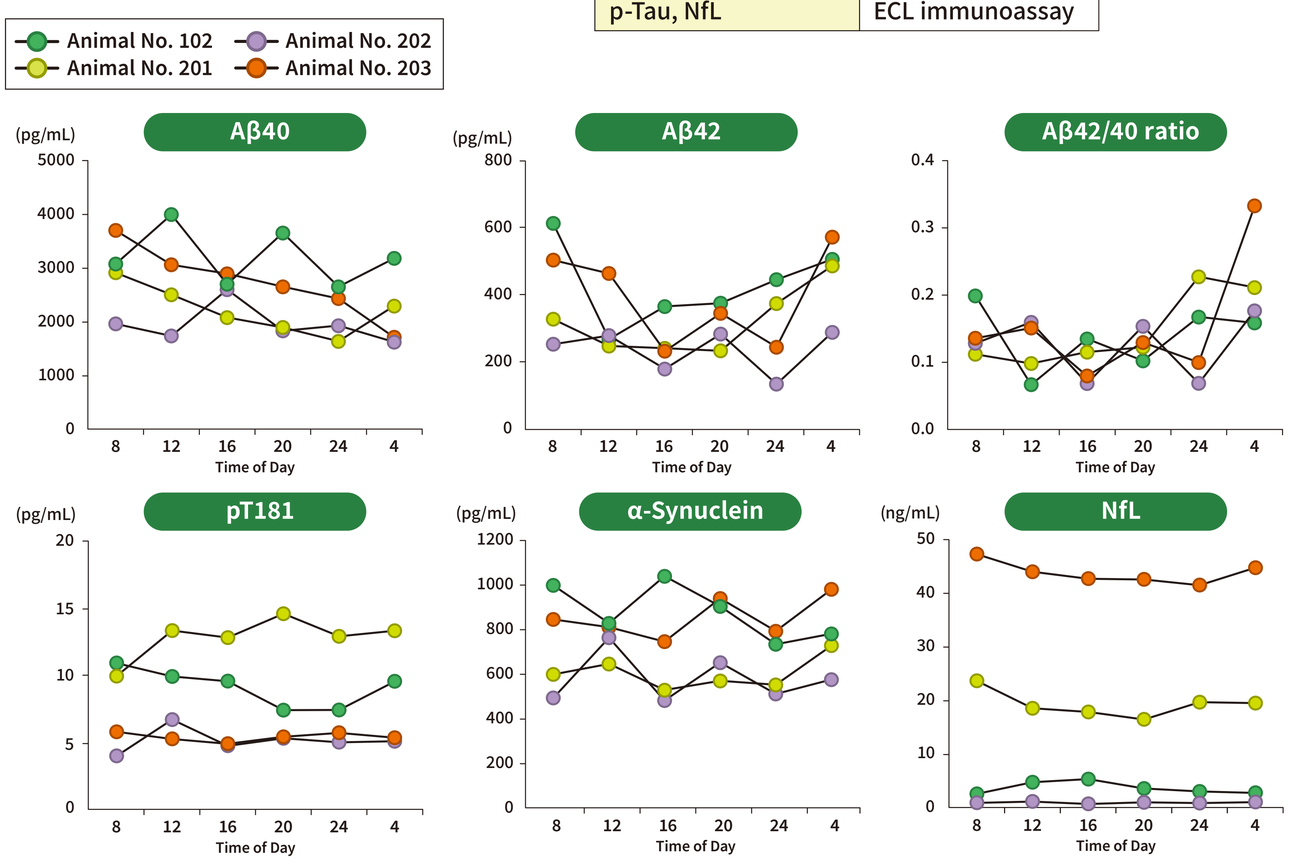


Evaluation items

Aβ40, 42, 42/40比, p-Tau	Alzheimer's disease, Dementia
α-Synuclein	Parkinson's disease
NfL	NfL—ALS, Neuroaxonal injury

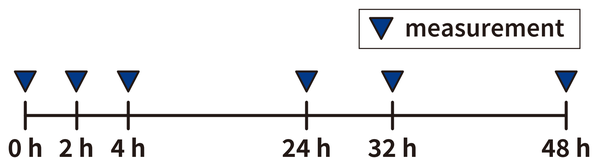
Assay method

Aβ40, 42, α-Synuclein	ELISA
p-Tau, NfL	ECL immunoassay

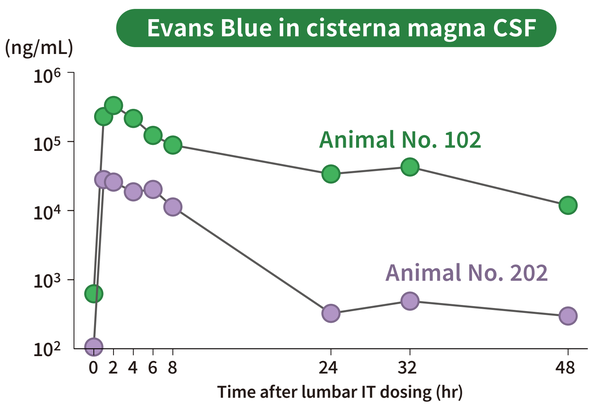


3 Evans Blue: Rostral Distribution Assessment

CSF samples were collected 1, 2, 4, 24, 32, and 48 hours after administration.

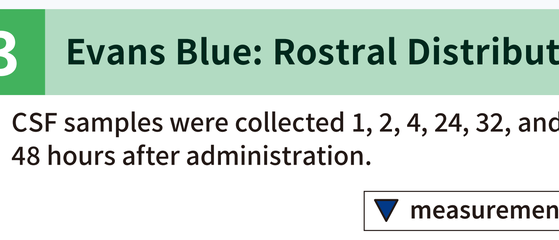


Evans Blue administered intrathecally at L5–6 was detected in cisterna magna CSF in a time-dependent manner.



4 NfL After Paclitaxel Dosing

Paclitaxel was administered on Days 0 and 7, and CSF samples were collected on Days 7 and 14.



CSF NfL changes after paclitaxel dosing were detected using this model, supporting its applicability for neurotoxicity biomarker assessment.

Daily general condition observations after paclitaxel dosing

Paclitaxel: Day 0 and Day 7/CSF: Day 7 and Day 14

Animal No.	Sex	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
102	M	+	++	++	+++	+++,a	+, a	–	–	–	–	–	–	–	–	–
201	F	–	–	–	+, a	++, b	+	+	++	+++	++, b	++	+++, a	+++, a	+++, a	+++, a
203	F	–	–	–	++	++	+	–	+	+	+++	++	++	+	++	–

No. 202 was treated as a reference value and was not included in this graph because of an exceptionally high individual response.

–: no remarkable findings
+: ≤1/4 residual food
++: ≤1/2 residual food
+++: ≥3/4 residual food
a: diarrhea
b: vomiting

References

Result 1: Ballesteros A, et al. Int J Toxicol. 2020;39(2):124–130.
Result 2: Lewczuk et al. World J Biol Psychiatry. 2018;19(4):244–328.
Result 2: Olsson B, et al. Lancet Neurol. 2016;15(7):673–684.
Result 4: Kim SH, et al. Front Oncol. 2022.

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