ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Professor of Clinical Neurosurgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Pediatric Neurosurgery

Editor
Frank Van Calenbergh, MD
University Hospitals; Leuven, Belgium

SNI
Open Access

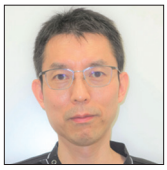
Original Article

Glial fibrillary acidic protein immunopositive neuroglial tissues with or without ependyma-lined canal in spinal lipoma of filar type: Relationship with retained medullary cord

Nobuya Murakami[1], Takato Morioka[2], Ai Kurogi[1], Satoshi O. Suzuki[3], Takafumi Shimogawa[4], Nobutaka Mukae[4], Koji Yoshimoto[4]

[1]Department of Neurosurgery, Fukuoka Children's Hospital, [2]Department of Neurosurgery, Hachisuga Hospital, Fukuoka, Japan, [3]Department of Psychiatry, Shourai Hospital, Karatsu, [4]Department of Neurosurgery, Kyushu University, Fukuoka, Japan.

E-mail: *Nobuya Murakami - murakami.n@fcho.jp; Takato Morioka - takatons1227@gmail.com; Ai Kurogi - aironron8282@gmail.com; Satoshi O. Suzuki - sosuzuki@shouraikai.jp; Takafumi Shimogawa - shimogawa28@gmail.com; Nobutaka Mukae - mukae@ns.med.kyushu-u.ac.jp; Koji Yoshimoto - yoshimoto.koji.315@m.kyushu-u.ac.jp



***Corresponding author:**
Nobuya Murakami,
Department of Neurosurgery,
Fukuoka Children's Hospital,
Fukuoka, Japan.

murakami.n@fcho.jp

Received: 11 June 2024
Accepted: 08 August 2024
Published: 13 September 2024

DOI
10.25259/SNI_458_2024

Quick Response Code:

ABSTRACT

Background: Retained medullary cord (RMC) and filar lipomas are believed to originate from secondary neurulation failure; filar lipomas are reported to histopathologically contain a central canal-like ependyma-lined lumen with surrounding neuroglial tissue with ependyma-lined central canal (NGT w/E-LC) as a remnant of the medullary cord, which is a characteristic histopathology of RMC. With the addition of glial fibrillary acidic protein (GFAP) immunostaining, we reported the presence of GFAP-positive NGT without E-LCs (NGT w/o E-LCs) in RMC and filar lipomas, and we believe that both have the same embryopathological significance.

Methods: We examined the frequency of GFAP-positive NGT, with or without E-LC, in 91 patients with filar lipoma.

Results: Eight patients (8.8%) had NGT w/E-LC, 25 patients (27.5%) had NGT w/o E-LC, and 18 patients (19.8%) had tiny NGT w/o E-LC that could only be identified by GFAP immunostaining. Combining these subgroups, 56% of the patients (n = 51) with filar lipoma had GFAP immunopositive NGT.

Conclusion: The fact that more than half of filar lipomas have NGT provides further evidence that filar lipoma and RMC can be considered consequences of a continuum of regression failure that occurs during late secondary neurulation.

Keywords: Closed neural tube defect, Secondary neurulation, Spinal dysraphism, Cord tethering, Embryopathology

INTRODUCTION

Retained medullary cord (RMC) is an entity of closed spinal dysraphism that is believed to originate from secondary neurulation failure.[16,17] The morphological feature of the RMC is a redundant non-functional cord-like structure (C-LS) continuous from the conus medullaris and extending to the dural cul-de-sac, which can cause neurological deficits by tethering.[5,7,14] Confirmation of the presence of non-functional C-LS with intraoperative neurophysiological

monitoring is important for the diagnosis of RMC.[7,16,18] The central feature in the histopathology of RMC is an ependyma-lined central canal with surrounding neuroglial tissues (neuroglial tissues with ependyma-lined central canal [NGT w/E-LC]), indicating a remnant of the cavitary medullary cord, which normally regresses, but can remain due to late arrest of secondary neurulation before the degenerative phase.[16,17]

NGT w/E-LC has been reported to be present in the filum. [2,4,19,21] and in spinal lipomas, including the filar and caudal types.[6,23] In our previous report, NGT w/E-LC was observed in 4 (17.4%) out of 23 patients with lipoma of filar type (filar lipoma) and 2 (15.4%) out of 13 patients with caudal types.[13] In another study, we showed that NGT w/E-LC was present at a higher rate (63.6%) in 11 patients with caudal-type lipoma by thorough histopathological examination of the resected whole non-functional portion of the lipoma.[10] Terminal lipomas, including filar- and caudal-type lipomas, are also believed to be secondary neurulation disorders,[11] which supports the idea of Pang *et al*.[16] that RMC and terminal lipomas have the same embryopathological basis and could be considered components of a continuum of regression failure disorders that occur during late secondary neurulation.

In contrast, solitary NGT without E-LC (NGT w/o E-LC) has been found in RMC and terminal lipoma;[7-10,15] however, little attention has been paid to the embryopathological significance of NGT w/o E-LC. One possible reason is that with routine hematoxylin and eosin (H&E) staining alone, a small portion of NGT can be missed, while the central canal is recognized and eventually underestimated.[9] With glial fibrillary acidic protein (GFAP) immunostaining, we found small NGT w/o E-LC in the non-functional C-LS of the RMC. Based on these findings, we believe that NGT w/o E-LC has the same embryopathological features as NGT w/E-LC.[9,10] Supporting the idea, we reported a case with filar lipoma in which GFAP immunopositive NGT w/o E-LC was also present in lipomatous tissues.[15] Here, we examined the frequency of GFAP-positive NGT, with or without E-LC, in 91 consecutive cases of filar lipoma and discussed the embryopathological relationship between filar lipoma and RMC.

MATERIALS AND METHODS

A retrospective analysis was performed on 91 patients with filar lipomas (43 boys and 48 girls) who underwent initial untethering surgery at Fukuoka Children's Hospital between September 2017 and February 2024. The median age at surgery was 2.9 years (range, 4 months to 20 years). Patients with spinal dysraphism attributed to first neurulation failure were excluded from the study. A diagnosis of filar lipoma was made from the findings of preoperative magnetic resonance imaging based and Arai's classification.[1]

Five patients with symptoms, such as leg pain or mild motor weakness, underwent untethering surgery. Before spinal fusion and correction surgery, 29 patients with scoliosis underwent preventive surgery. Sixteen patients with low-lying conus (below L2/3) underwent preventive surgery. Other patients underwent preventive surgery after discussions with their parents.

In principle, minimally invasive surgery is performed through preexisting spina bifida or single-level laminoplastic laminotomy at L5 or S1. Intraoperatively, the fatty filum was segregated using a rubber dam and stimulated with a current intensity of up to 3 mA to confirm that it was non-functional. The filum was resected as a column. Surgical specimens were placed in formalin and performed with H&E staining and immunostaining for GFAP.

The clinical and neuroradiological findings have been analyzed as in previous clinical studies on filar lipomas.[3,22] When the patient had congenital anomalies, such as VACTERL and Klippel-Feil syndrome, they were defined as syndromic. Statistical analysis was performed using Fisher's exact test or the Kruskal–Wallis test. (R version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria), and a significance level of $P < 0.05$ was considered for all analyses.

RESULTS

Eight patients (8.8% of the total patients) had NGT w/E-LC [Figure 1], which was located in the periphery, not in the center of the fibroadipose tissues. NGT w/o E-LC was observed [Figure 2] in 25 patients (27.5%). In 18 patients (19.8%), tiny NGT without E-LC that could only be identified by immunostaining with GFAP was observed [Figure 3]. Combined, 43 patients (47.3%) had solitary NGT. These NGTs are also located on the periphery of fibroadipose tissue. Therefore, combining these three subgroups, 56% of the patients ($n = 51$) with filar lipoma had GFAP immunopositive NGT, while the remaining 44% of the patients ($n = 40$) did not have NGT [Figure 4].

We compared the clinical features of patients with and without NGT, including age at surgery, syndromic status, preoperative symptoms, cutaneous signs, and surgery for scoliosis. The age at surgery of patients with NGT (median, 1.7 years; range, 4 months to 16 years) was significantly younger than those without NGT (median, 8.5 years; range, 6 months to 20 years). This was because the w/o NGT group included more patients before scoliosis surgery, who were all aged ≥6 years, than the w/NGT group. There were no significant differences in other items.

Morphological features, including conus level, diameter of the fatty filum, and association of filar cysts or syrinx, were also assessed between the w/and w/o NGT groups, and there

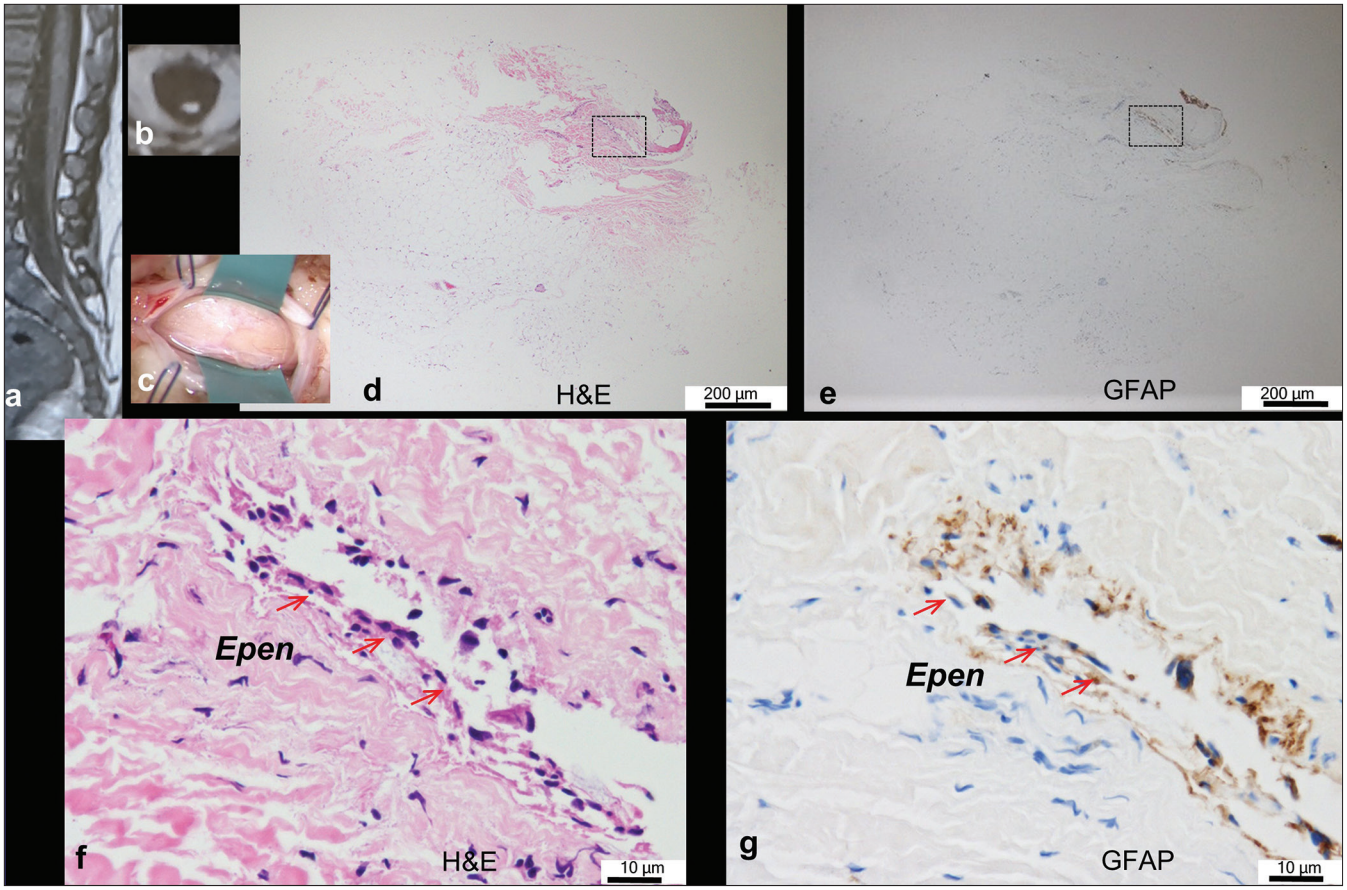


Figure 1: Typical case of neuroglial tissue with ependyma-lined central canal (there are eight similar cases in total). (a, b) Sagittal and axial views of the T1-weighted image show a fatty filum with a low-lying spinal cord tapering to the dural cul-de-sac. (c) The intraoperative photograph shows the lipoma of filar type with a diameter of 4.0 mm through laminotomy at L5. (d-g) Histopathological findings of the transverse sections of the lipoma stained with hematoxylin and eosin (H&E; (d, f)) and immunostained with glial fibrillary acidic protein ((GFAP); (e, g)). Higher-magnification views of the area are indicated by dashed squares in (d) and (e). A single ependyma-lined canal (Epen; red arrows in (f) and (g)) with surrounding neuroglial tissues is embedded in the periphery of lipomatous fibroadipose tissue.

were no significant differences in these parameters. From the perspective of the fatty filum diameter, an extremely thick filum (≥4.0 mm) was exclusively involved in the NGT w/E-LC and NGT w/o E-LC groups, in which there was a certain amount of NGT, although other thinner filum was involved in various types [Figure 5].

DISCUSSION

The present study showed that NGT w/E-LC was found in 8.8% of 91 patients with filar lipoma, while in our previous report, E-LC w/NGT was observed in 4 (17.4%) out of 23 patients with filar lipoma.[13] This slight difference in the detection rate was probably due to the difference in population size, and we believe it to be approximately 10%.

The most notable finding of the present study was that NGT w/o E-LC was observed frequently (47.3%). Adding the NGT w/E-LC to this, GFAP immunopositive NGT was observed in 56% of filar lipomas. The possible reason why most NGT lack E-LC is that small islands of E-LC may have been missed during routine sectioning of the surgical specimen, as previously described[7,8] because the NGT was located in the periphery, not in the center of lipomatous tissues and the C-LS of the RMC in the present study and our previous reports.[7-10,12-14,20] The second possible reason to explain the existence of the NGT without the E-LC is the difference in the degree of regression of the contents of the medullary cord; that is, the E-LC might have regressed earlier than that of the NGT. However, there is no evidence for this. The third possible reason is that resection of the entire lipoma could not be performed due to limited operative exposure, and only a small part of the lipoma was submitted to histological examination, leading to the loss of a small part of the E-LC. The finding of the present study that extremely thick fatty filum tends to contain NGT and E-LC may support this idea.

There were no significant differences in clinical background, except for age at operation, between the groups with and

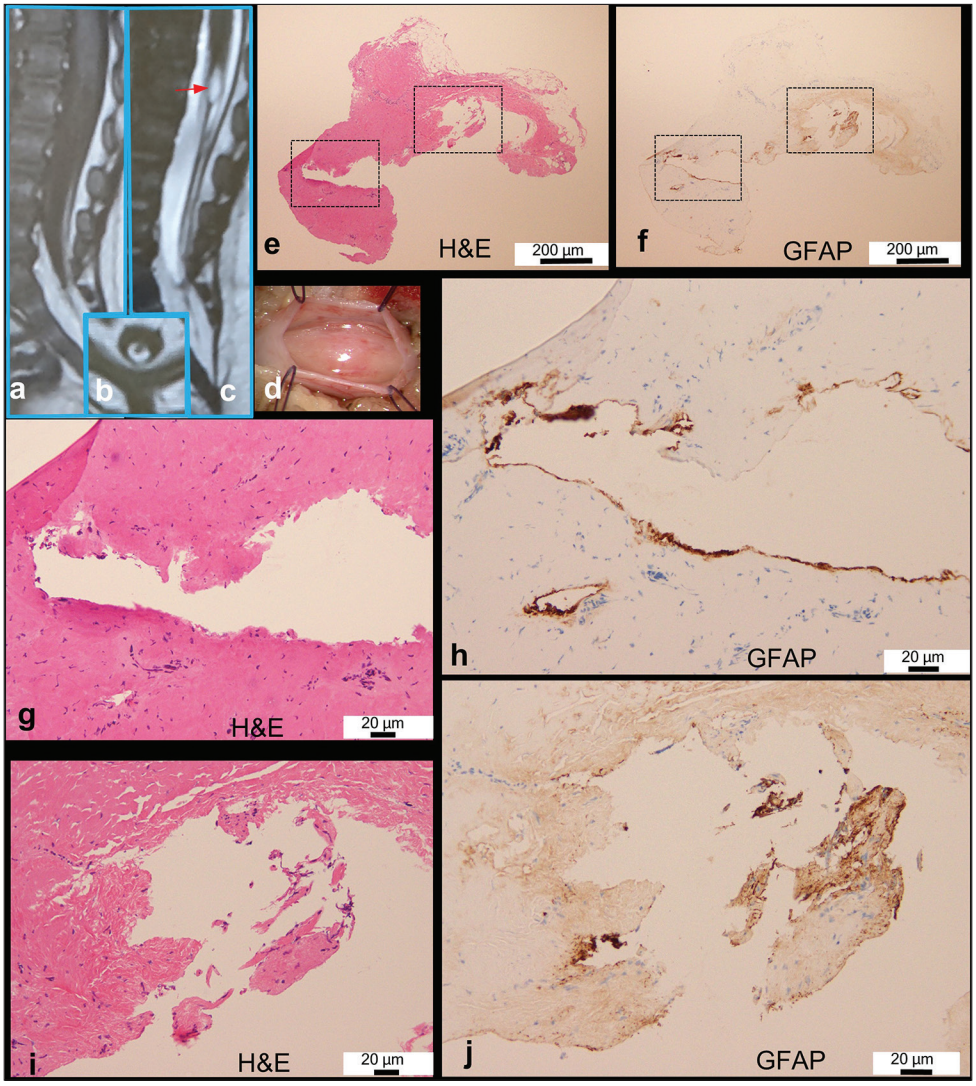


Figure 2: Typical case of neuroglial tissue without ependyma-lined central canal (there are 25 similar cases in total). (a,b) Sagittal and axial views of the T1-weighted image show fatty filum. (c) Sagittal views of three-dimensional heavily T2-weighted imaging show a filar cyst (red arrow). (d) Intraoperative photograph showing the filar lipoma with a diameter of 4.0 mm through the laminotomy at L5. (e-j) Histopathological findings of the transverse sections of the lipoma stained with hematoxylin and eosin (H&E; e, g, i) and immunostained with glial fibrillary acidic protein (GFAP; f, h, j). Higher-magnification views of the area are indicated by dashed squares in (e) and (f). Neuroglial tissues are focally attached to fibroadipose tissue, which is clearly delineated by GFAP but barely by H&E. There is no central canal lined by ependymal cells.

without NGT. The finding that NGT is absent more often in elderly patients may suggest age-dependent degeneration of the filum, although the detailed mechanism is unknown.

As we previously reported cases of large filar cysts associated with terminal lipomas, including filar and caudal types, which are histopathologically cystic dilatations of the E-LC with a surrounding NGT, indicating cystic RMC,[12] we were interested in the association of filar cysts with NGT. The present study revealed that the presence or absence of filar cysts was not relevant to NGT, possibly because the filar cysts were relatively small and rostrally positioned, as shown in Figure 2. There were also no significant differences in other neuroradiological morphological features.

The terminology for RMC and lipoma is based on their embryological and morphological background, respectively.[9,10] Considering the amount of adipose tissue surrounding the neuroglial core, when the adipose tissue is sufficiently large to demonstrate hyperintensity on a T1-weighted image, the diagnosis is filar lipoma; when the

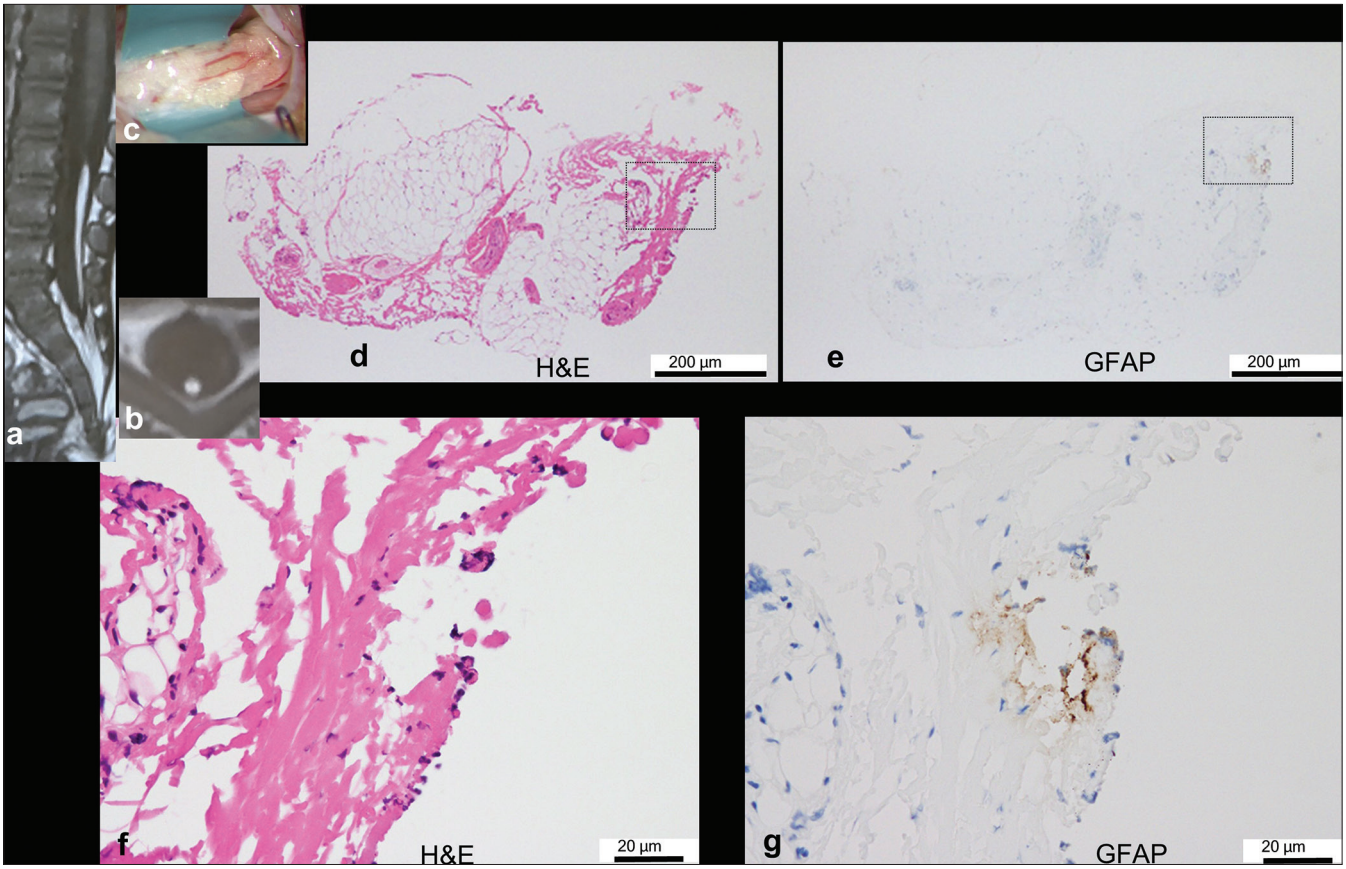


Figure 3: Typical case of tiny neuroglial tissue (there are 18 similar cases in total). (a, b) Sagittal and axial views of the T1-weighted image show fatty filum with lower-lying conus. (c) Intraoperative photograph showing filar lipoma with a diameter of 1.5 mm through laminotomy at S1. (d-g) Histopathological findings of the transverse sections of the lipoma stained with hematoxylin and eosin (H&E; d, f) and immunostained with glial fibrillary acidic protein (GFAP; e, g). Higher-magnification views of the area are indicated by dashed squares in (d) and (e). Tiny neuroglial tissues are attached to the periphery of fibroadipose tissue, which can only be detected by GFAP but not by H&E. There is no central canal lined with ependymal cells.

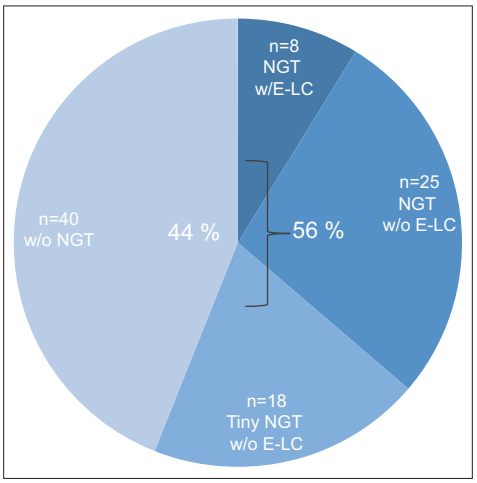


Figure 4: Rate of cases with filar lipoma containing glial fibrillary acidic protein immunopositive neuroglial tissues (NGT) with or without an ependyma-lined canal (w/E-LC, w/o E-LC) in surgical specimens.

amount of adipose tissue is small, the diagnosis is RMC. The present study revealed the presence of NGT in more than half of cases of filar lipoma, further confirming the idea that filar lipoma and RMC entities can be considered consequences of a continuum of regression failure that occurs during late secondary neurulation.

This study has several limitations. First, as mentioned in the Introduction, it has been reported that normal filum also contains NGT[2,19], although which exact incidence has not been known. Therefore, it may be necessary to interpret cautiously the result of the high incidence of the association of NGT with fatty filum. Future studies will need to compare the exact incidence of NGT in normal and fatty filum and verify the embryological significance of NGT in the filum. Second, in this study, since the filum was resected at the L5 or S1 level, we were unable to clarify the relationship between the presence of NGT and the level of the filum.

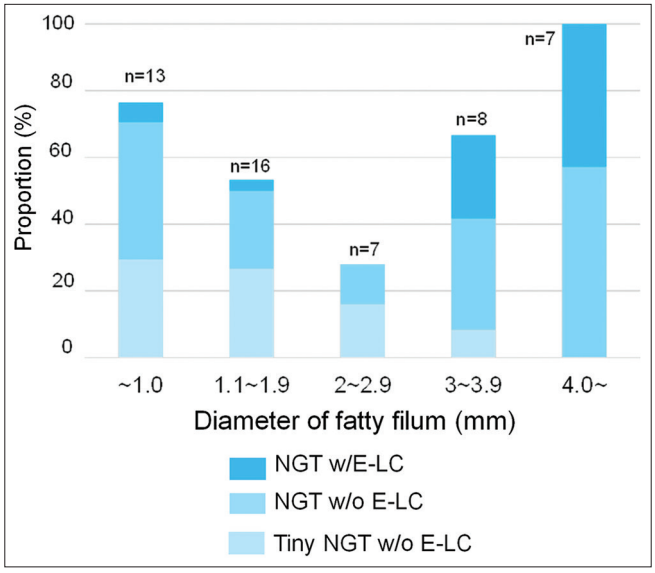


Figure 5: The proportion of cases containing neuroglial tissue (NGT) to total filar lipoma cases classified by the diameter of its fatty filum, in which the stacked bar chart indicates the proportion of NGT with the ependyma-lined central canal (w/E-LC), NGT w/o E-LC, and tiny NGT w/o E-LC.

CONCLUSION

Although further study to improve the above limitations will be needed, the 56% incidence of the association of GFAP immunopositive NGT with filar lipoma is believed to be due to secondary neurulation failure with the same embryological background as RMC. These results may provide a deeper understanding of the embryogenic background of lumbosacral spinal lipomas.

Ethical approval

The research/study approved by the Institutional Review Board at Fukuoka Children's Hospital, number 2021-713, dated July 5, 2021.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Arai H, Sato K, Okuda O, Miyajima M, Hishii M, Nakanishi H, *et al.* Surgical experience of 120 patients with lumbosacral lipomas. Acta Neurochir (Wien) 2001;143:857-64.
2. Choi BH, Kim RC, Suzuki M, Choe W. The ventriculus terminalis and filum terminale of the human spinal cord. Hum Pathol 1992;23:916-20.
3. Cools MJ, Al-Holou WN, Stetler WR Jr., Wilson TJ, Muraszko KM, Ibrahim M, *et al.* Filum terminale lipomas: Imaging prevalence, natural history, and conus position. J Neurosurg Pediatr 2014;13:559-67.
4. Durdağ E, Börcek PB, Öcal Ö, Börcek AÖ, Emmez H, Baykaner MK. Pathological evaluation of the filum terminale tissue after surgical excision. Childs Nerv Syst 2015;31:759-63.
5. Kim KH, Lee JY, Wang KC. Secondary neurulation defects-1: Retained medullary cord. J Korean Neurosurg Soc 2020;63:314-20.
6. Lellouch-Tubiana A, Zerah M, Catala M, Brousse N, Kahn AP. Congenital intraspinal lipomas: Histological analysis of 234 cases and review of the literature. Pediatr Dev Pathol 1999;2:346-52.
7. Morioka T, Murakami N, Kanata A, Tsukamoto H, Suzuki SO. Retained medullary cord with sacral subcutaneous meningocele and congenital dermal sinus. Childs Nerv Syst 2020;36:423-7.
8. Morioka T, Murakami N, Ichiyama M, Kusuda T, Suzuki SO. Congenital dermal sinus elements in each tethering stalk of coexisting thoracic limited dorsal myeloschisis and retained medullary cord. Pediatr Neurosurg 2020;55:380-7.
9. Morioka T, Murakami N, Suzuki SO, Mukae N, Shimogawa T, Kurogi A, *et al.* Surgical histopathology of a filar anomaly as an additional tethering element associated with closed spinal dysraphism of primary neurulation failure. Surg Neurol Int 2021;12:373.
10. Morioka T, Murakami N, Kurogi A, Mukae N, Shimogawa T, Shono T, *et al.* Embryopathological relationship between retained medullary cord and caudal spinal lipoma. Interdiscip Neurosurg 2022;29:101534.
11. Morota N, Ihara S, Ogiwara H. New classification of spinal lipomas based on embryonic stage. J Neurosurg Pediatr 2017;19:428-39.
12. Mukae N, Morioka T, Suzuki SO, Murakami N, Shimogawa T, Kanata A, *et al.* Two Cases of large filar cyst associated with terminal lipoma: Relationship with retained medullary cord. World Neurosurg 2020;142:294-8.

13. Murakami N, Morioka T, Shimogawa T, Mukae N, Inoha S, Sasaguri T, *et al.* Ependyma-lined canal with surrounding neuroglial tissues in lumbosacral lipomatous malformations: Relationship with retained medullary cord. Pediatr Neurosurg 2018;53:387-394.
14. Murakami N, Morioka T, Shimogawa T, Hashiguchi K, Mukae N, Uchihashi K, *et al.* Retained medullary cord extending to a sacral subcutaneous meningocele. Childs Nerv Syst 2018;34:527-33.
15. Oketani H, Harimaya K, Ono T, Terado K, Inoha S, Suzuki SO, *et al.* A presenile patient with filar lipoma who developed tethered spinal cord syndrome triggered by lumbar canal stenosis. NMC Case Rep J 2023;10:109-13.
16. Pang D, Zovickian J, Moes GS. Retained medullary cord in humans: Late arrest of secondary neurulation. Neurosurgery 2011;68:1500-19.
17. Pang D, Chong S, Wang KC. Secondary neurulation defects-1: Thickened filum terminale, retained medullary cord. In: Di Rocco C, Pang D, Rutka JT, editors. Textbook of pediatric neurosurgery. 1st ed. Switzerland: Springer; 2020.
18. Sala F, Barone G, Tramontano V, Gallo P, Ghimenton C. Retained medullary cord confirmed by intraoperative neurophysiological mapping. Childs Nerv Syst 2014;30:1287-91.
19. Selçuki M, Vatansever S, Inan S, Erdemli E, Baĝdatoĝlu C, Polat A. Is a filum terminale with a normal appearance really normal? Childs Nerv Syst 2003;19:3-10.
20. Shirozu N, Morioka T, Inoha S, Imamoto N, Sasaguri T. Enlargement of sacral subcutaneous meningocele associated with retained medullary cord. Childs Nerv Syst 2018; 34:1785-90.
21. Sim J, Shim Y, Kim KH, Kim SK, Lee JY. Features of the filum terminale in tethered cord syndrome with focus on pathology. J Korean Neurosurg Soc 2021;64:585-91.
22. Usami K, Lallemant P, Roujeau T, James S, Beccaria K, Levy R, *et al.* Spinal lipoma of the filum terminale: Review of 174 consecutive patients. Childs Nerv Syst 2016;32:1265-72.
23. Walsh JW, Markesbery WR. Histological features of congenital lipomas of the lower spinal canal. J Neurosurg 1980;52:564-9.

How to cite this article: Murakami N, Morioka T, Kurogi A, Suzuki SO, Shimogawa T, Mukae N, *et al*. Glial fibrillary acidic protein immunopositive neuroglial tissues with or without ependyma-lined canal in spinal lipoma of filar type: Relationship with retained medullary cord. Surg Neurol Int. 2024;15:326. doi: 10.25259/SNI_458_2024