

Clinical Features and Ultrasound Findings of a Rare Musculoskeletal System Disease—neuromuscular Choristomas

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Abstract

Background: Neuromuscular choristomas (NMCs) as exquisitely rare developmental lesions have previously been established associated with recurrent fibromatosis after surgery, led to multiple operations, or even amputation. Yet, the report about ultrasound imaging features and clinical conditions of NMCs was rare. The purpose of this study was to describe the ultrasound features and clinical analysis of NMCs to provide suggestions to the optimal management strategy.

Methods: From 2020 September to 2021 September, 7 patients with a confirmed diagnosis of NMC who underwent ultrasound examination in our department were enrolled into our study. Physical examinations were performed to detect motor deficit, sensory deficit, neuropathic pain, limb undergrowth, muscular atrophy, cavus foot and bone dysplasia. Ultrasound imaging were performed and investigated in both involved nerve and neuromuscular choristomas associated desmoid-type fibromatosis (NMC-DTF). All patients had a definite history and regular follow up. The clinical course, physical examinations, ultrasound features and pathologic results of NMC patients were analyzed.

Results: Seven patients with an average age of 7.0 ± 7.2 years (range: 2-22 years) were enrolled into our study. Nerves involved included the sciatic nerve (6 cases) and the brachial plexus (1 case). 6 patients (85.7%) presented with manifestations of limb undergrowth, 6 (85.7%) with muscular atrophy, and 5 (71.4%) with cavus foot deformity. Based upon ultrasound findings, all visible involved nerve segments presented with hypoechoic and fusiform enlargement with intraneural skeletal muscle elements. Five patients (71.4%) had NMC-DTFs at the site of the affected nerve. All NMC-DTFs were shown as hypoechoic solid lesion adjacent to the nerve and well-circumscribed. In the subset of surgery group, all 5 patients presented with progression to NMC-DTFs at the site of the NMCs. No fibromatosis was detected in the other two non-surgery patients.

Conclusions: Understanding of the typical ultrasound features and clinical associated conditions would help to early diagnose the rare disease. When a potential diagnosis is made, invasive procedure like biopsy or resection might be not a good choice given frequent complication by aggressive recurrence.

Background

Neuromuscular choristomas (NMCs), previously known as benign triton tumors, are rare congenital lesions with differentiated mature skeletal muscle tissue found within peripheral nerve fascicles.[1–5] Patients often present with NMCs during childhood or as teenagers, but occasionally as adults. NMCs commonly affect the sciatic nerve (the most common location of NMC), or the brachial plexus but have been known to involve other sites, such as the trigeminal nerve[6], oculomotor nerve[7, 8], or the internal auditory meatus[9]. Histologically, NMC is characterized by the presence of mature muscle fibers inside the endoneurium, intercalated among nerve fibers[10]. In most of the reported cases[11–14], the lesion was solitary, associated with a major nerve, and composed of disorganized mature skeletal muscle fibers admixed with nerve twigs. Desmoid-type fibromatosis(DTF) at the site of the NMC may occur and seems to be incited by surgical biopsy[15, 16]. Aggressive neuromuscular choristomas associated desmoid-type fibromatosis (NMC-DTF) often requires multiple operations, radiation and chemotherapy, or even amputation. So, it is important to identify the clinical and imaging features of NMCs to avoid invasive procedure like biopsy or resection and refrain from aggressive fibromatosis. The purpose of this study was to describe the clinical and ultrasound features of NMCs and to determine the optimal management strategy.

Methods

This prospective study was approved by the Institutional Review Board, and written informed consent was waived. All methods were carried out in accordance with relevant guidelines and regulations.

Patients

After encountering a case of DTF found to have an occult NMC, we performed a prospective study to confirm a new diagnose of underlying NMC. From 2020 September to 2021 September, 235 consecutive patients (younger than 30 years old) with abnormal thickening of sciatic nerve and brachial plexus underwent ultrasound examination in our center. Among them, seven patients with a diagnosis of NMC and a definite history were enrolled in our study. The inclusion criteria were shown as follows: (1) Pathology-proven or clinicoradiological NMC diagnosis; (2) Fusiform enlargement of sciatic nerve or brachial plexus; (3) Intraneural soft-tissue components with echo intensity comparable to surrounding skeletal muscle; (4) Patients under the age of 30 years.

The exclusion criteria for this study included: (1) Enlargement of sciatic nerve or brachial plexus caused by trauma or surgery; (2) Other peripheral nerve tumors such as neurofibroma, schwannoma, perineurioma and lipomatosis; (3) Missed follow up.

Clinical and physical examination

The clinical and physical examinations were collected including age, sex, NMC location, the presence of motor deficit, sensory deficit, neuropathic pain, limb undergrowth, muscular atrophy, cavus foot, bone dysplasia.

Ultrasonography

All enrolled patients received ultrasound examination to evaluate the disease features and progression at each follow-up. All sonographic examinations were carried out by one of two radiologists (W.G., T.C.) with more than 10 years of experience in musculoskeletal ultrasound procedures. The ultrasound features evaluated including: NMC location, morphology and internal characteristics of involved nerves, presence of NMC-DTF, tumor size, margin, echo intensity, Color Doppler blood flow grade, spatial relationship between NMC-DTF and involved nerves and local recurrence and/or progression.

Due to some patients (especially for recurrent NMC-DTFs) were not the first time for medical consultations and/or treatment in our institution, we also collected the information of past history including operation and postoperative course, pathological results, treatment process, recurrence times, neurologic motor and sensory examination at each follow-up. All the clinical course, physical examinations, ultrasound features and available pathologic results of NMC patients were reviewed and evaluated in detail.

Results

There were 4 males and 3 females, with an average age of 6.3 ± 8.0 years (range: 1-22 years) enrolled into our study. Among the seven patients, five patients were diagnosed on the basis of a nerve biopsy or/and surgery, two patients were diagnosed due to the presence of characteristic clinical and imaging features of an NMC and therefore did not undergo a nerve biopsy based upon current "no touch" principle. Nerves involved included the sciatic nerve (6 cases, 85.7%) and the brachial plexus (1 case, 14.3%) .

Clinical presentation and physical examination

Clinical data were presented in table 1 and figures 1-4. All the NMC-DTFs were hard and firm on palpation. Motor deficit occurred in 4 patients (57.1%), the main manifestation is foot drop and weakness of toe extension (common peroneal nerve injury). Sensory deficit occurred in 1 patients (14.3%), neuropathic pain was reported in 3 patients (42.9%). 6 patients (85.7%) presented with manifestations of limb undergrowth, 6 (85.7%) with muscular atrophy, and 5 (71.4%) with cavus foot deformity. Bone dysplasia was not found among the seven patients.

Ultrasound imaging features

All ultrasound imaging features of NMC/NMC-DTF were summarized in table 2. Based upon ultrasound findings, all visible NMC involved nerve segments presented with hypoechoic and fusiform enlargement (Figure 1,2,4), The echo intensity of intraneural soft-tissue components was comparable to surrounding skeletal muscle. One affected nerve segment was invisible due to massive NMC-DTF (Figure 3). The structure of perineurium and epineurium in affected nerve was clear. The cross-section of affected nerves still showed cribriform pattern as same as the normal nerve, which was different from other peripheral nerve tumors (i.e. neurofibroma, schwannoma and perineurioma).

Among 7 NMCs, five patients (71.4%) along with NMC-DTFs at the site of the affected nerve (all performed surgical resection or biopsy before). No lesion grew to involve a new neighboring nerve. All NMC-DTFs were shown as hypoechoic solid lesion adjacent to the nerve with irregular shape and well-circumscribed. Color Doppler blood flow grade was 1-2. Among the five NMC-DTFs, three NMC-DTFs enveloped the proximal adjacent sciatic nerve (Patient #2,3,5). One case enveloped the distal branches of involved sciatic nerve (Patient #1). One occurred in the brachial plexus, the tumor was close to the vertebral body, the structure of the proximal nerve root was invisible in ultrasound (Patient #4). Postoperative pathology confirmed that the brachial plexus nerve root was running through the inside of the tumor, which could not be distinguished from the tumor.

Pathological findings

Five patients were diagnosed NMCs by nerve biopsy (1 patient) and/or previous surgical resection of NMC/NMC-DTFs (4 patients). Among the five available pathological results, all NMCs were composed of varying amounts of mature skeletal muscle fibers intercalating among peripheral nerve fascicles. Based upon immunohistochemical stains, all NMCs showed scattered (myo) fibroblasts with aberrant nuclear localization of β -catenin protein (Figure 1-3). One case was also positive for a CTNNB1 p.S45F mutation (Figure 2; patient #3).

Clinical course and follow-up

Clinical course and follow-up information were presented in table 3. The mean clinical follow-up time after enrollment was 9.4 months, with a range of 6-12 months. Progression of motor deficit and muscles atrophy were observed in 2 (28.6%) patients. One patient (14.3%) had progression of limb undergrowth. Tumor recurrence was detected in two patients (28.6%) at 3, 8 months since first surgical resection, respectively. One of them performed three-times tumor resection and a course radiotherapy. The other one performed chemotherapy (twice) and high intensity focused ultrasound knife (HIFU) treatment for six times, failed to control the tumor progression and finally lead to above-knee amputation (Figure 2).

In the subset of tumor surgery group, all 5 patients presented with progression of NMC-DTFs at the site of the NMCs. No fibromatosis was detected in the other two non-surgery patients and the disease was stable during the observation period (Figure 5).

Discussion

Neuromuscular choristoma (NMC) as a rare developmental lesion typically involved major nerves or plexuses, most commonly affected sciatic nerve and brachial plexus[1, 4, 5, 12, 14, 17, 18]. It was characterized by the biomorphic composition of heterotopic skeletal muscle fibers within peripheral nerve. Unlike hamartomas, it contains mature muscle fibers in an aberrant location and may be best classified as a form of heterotopia[1]. Previous studies have reported that desmoid-type fibromatosis (DTF) at the site of the NMC may be incited by surgical resection/biopsy. Although it does not undergo metastatic transformation, NMC-DTF is locally aggressive and infiltrative, frequently encompassing neurovascular structures and lead to local recurrence after resection[16, 19].

Previous studies have reported that patients with NMC typically present in childhood with a localized neuropathy or plexopathy and manifestations of chronic undergrowth in the affected nerve's territory[16]. In our study, all patients were under 25 years old, most under ten (85.7%). The detection rate of motor deficit, neuropathic pain, limb undergrowth, muscular atrophy, cavus foot deformity was 71.4%, 42.9%, 71.4%, 85.7%, 71.4%, respectively. The main manifestation of

motor deficit was foot drop and weakness of toe extension due to common peroneal nerve injury. All of these symptoms were in the territory of the affected nerve.

Ultrasound examination could help establish the diagnosis of NMC without the need for a biopsy. Based upon our findings, all visible involved nerve segments presented with hypoechoic and fusiform enlargement. The structure of perineurium and epineurium in affected nerve was clear. Most importantly, the echo intensity of intraneural soft-tissue elements was comparable to surrounding skeletal muscle, and the cross-section of affected nerves still showed cribriform pattern as same as the normal nerve. It was consistent with NMC pathological structure, since all NMCs were composed of varying amounts of mature skeletal muscle fibers intercalating among peripheral nerve fascicles. It may help us differentiate NMCs from other peripheral nerve tumors (i.e. neurofibroma, schwannoma and perineurioma). All NMC-DTFs were contiguous and shown as hypoechoic solid lesion adjacent to the enlarged nerve with irregular shape. All tumors occurred at the site of the NMC-affected nerve and no lesion grew to involve any other anatomic site, which was consistent with previous reports[16].

In all five pathologically confirmed cases, we observed characteristic histologic features of NMC: varying amounts of mature skeletal muscle fibers inside the endoneurium, intercalated among peripheral nerve fascicles, resulting in expansion of the affected nerve segment[10]. Based upon re-review of immunohistochemical stains, all showed aberrant nuclear localization of beta-catenin protein, which is an established indicator of activating CTNNB1 mutations (the gene encoding beta-catenin protein)[16, 20, 21]. Previous studies have demonstrated that NMC and NMC-DTF both harbor identical mutations in CTNNB1, particularly CTNNB1 p.S45F, a specific CTNNB1 mutation that has been associated with a more aggressive clinical behavior[20, 21]. In our study, the positive expression rate of beta-catenin protein was 100% in surgical pathologically confirmed patients. One case was also positive for a CTNNB1 p.S45F mutation and eventually led to an above-knee amputation. It may be one reason that all surgical resection patients presented with progression to NMC-DTFs and half of them had local recurrence. This result implied that if a pathologic diagnosis of NMC was obtained, follow-up studies may be warranted to assess for development of aggressive fibromatosis. And for patients with NMC, beta-catenin protein expression (CTNNB1 mutation, particularly CTNNB1 p.S45F) should be detected for a better outcome.

In our study, most of the patients came for consultation due to recurrent DTF and were found to have an occult underlying NMC. We agreed with the opinion that the coexistence of NMC may be under-recognized in patients with extremity DTF[22]. Based upon our course review and follow-up, all patients underwent surgery were presented with progression to NMC-DTFs at the site of the NMCs, while no fibromatosis was detected in non-surgery patients. Previous studies have suggested that the potential for fibromatosis occurring after surgery might lead to “no touch” approach when NMC is suspected, which means the diagnosis should be based solely on clinical and imaging criteria[1, 22, 23]. Although the natural history and true incidence of NMC and NMC-DTF remains unknown, our study favors the principle that for NMC patients, the diagnosis of NMCs is thought to be possible prior to biopsy or resection based on the unique and characteristic ultrasound findings with consistent clinical findings. On the other hand, peripheral nerves should be scrutinized carefully on imaging examination in all patients (especially for young patients) with DTF of the extremities to avoid missed diagnosis of NMC as this may have different follow-up and treatment strategy[16]. Also, the advantage of ultrasound application is that for young children, there is no need for sedation and could monitor repeatedly without harmful radiation. Therefore, an accurate diagnosis based on ultrasound findings may dissuade the clinician from proceeding with invasive procedure, and it may be necessary to follow up closely for the development of NMC-DTFs[24].

For patients with NMC-DTF, the correct treatment algorithm remains unknown. In the subset of our tumor surgery group, all 5 patients presented with progression of NMC-DTFs at the site of the NMCs. Previous studies supported that the mainstay of treatment for NMC-associated DTF could be nonsurgical management including loco-regional chemotherapy, exclusive radiation, systemic chemotherapy, and/or targeted therapy[22]. Further study may be needed for the best treatment of NMC-DTF.

Our study has several limitations. First, this study was small cohort due to rare of NMCs. More clinical studies and radiologic examinations may be performed to better recognize this disease. Secondly, pathological confirmation of the NMC was obtained in 5 cases, two patients lack of pathological diagnosis based on our current “no-touch” principle, it may require longer follow-up to demonstrate the features and progression of NMCs. More features should be assessed by long-term prospective follow-up of large numbers of people.

Conclusions

In conclusion, NMC as a rare developmental disease requires an accurate diagnosis in the right clinical setting. Understanding of the typical ultrasound features and clinical associated conditions would help to early diagnose and make recommendations for the treatment of NMC. Based on our experience and literatures, the “no touch” principle to the involved nerve might be an optimal suggestion to the occurrence of NMC in childhood.

Abbreviations

NMC: Neuromuscular choristomas; DTF: Desmoid-type fibromatosis; NMC-DTF: Neuromuscular choristomas associated desmoid-type fibromatosis; HIFU: High intensity focused ultrasound knife

Declarations

Ethics approval and consent to participate

This study had been approved by Peking university cancer hospital institutional review board (IRB-2018KT34). Written informed consent was waived.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from all the patients/parents.

Availability of data and materials

All the data needed to achieve the conclusion are contained within the paper. The raw data cannot be shared publicly due to ethical reason.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WG and TC performed ultrasound examination and investigated imaging features. SFW and SLC helped to collect the data, perform physical examination and follow-up. HW wrote the draft version of this paper, analyzed the data and revised it with corresponding author. WY and TC helped to analyze the data, revised the paper and gave some important opinions about this rare disease. All authors have read and approved the manuscript.

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Tables

Table 1. Clinical and physical examination of NMC.

Patient	Age/Sex	Location	Side	Motor deficit	Sensory deficit	Neuropathic pain	Limb undergrowth	Muscular atrophy	Cavus foot	Bone dysplasia
1	22/F	sciatic nerve	Left	N	N	Y	Y	Y	Y	N
2	2/M	sciatic nerve	Right	Y	Un	Un	Y	Y	Y	N
3	6/M	sciatic nerve	Left	Y	Y	Y	Y	Y	Y	N
4	10/F	brachial plexus	Left	N	N	Y	N	N	N	N
5	2/M	sciatic nerve	Right	Y	Un	Un	Y	Y	Y	N
6	4/M	sciatic nerve	Left	N	N	N	Y	Y	Y	N
7	3/F	sciatic nerve	Right	Y	N	N	Y	Y	N	N

Note: NMC=neuromuscular choristomas; Y=yes; N=no; Un=unknown due to young ages.

Table 2. Ultrasound imaging features of NMC/NMC-DTF.

Patient	Age/Sex	Location	Morphology of involved nerve	Transformation to DTF	NMC-DTF size (cm)	NMC-DTF margin	NMC-DTF echo intensity and morphology	CDFI grade	Spatial relationship between NMC-DTF and involved nerves	Loc recu
1	22/F	sciatic nerve	Hypoechoic, fusiform enlargement	Yes	12.6×6.3×3.4	Well-circumscribed	Hypoechoic solid lesion, irregular shape	1-2	NMC-DTF envelops the branches of the left sciatic nerve	No
2	2/M	sciatic nerve	Hypoechoic, fusiform enlargement	Yes	13.6×4.4×3.8	Well-circumscribed	Hypoechoic solid lesion, irregular shape	1-2	NMC-DTF envelops the proximal adjacent nerve	No
3	6/M	sciatic nerve	Hypoechoic, fusiform enlargement	Yes	24×17×12	Well-circumscribed	Hypoechoic solid lesion, irregular shape	1-2	NMC-DTF envelops the proximal adjacent nerve	Two
4	10/F	brachial plexus	Nerve invisible due to massive NMC-DTF	Yes	5.5×5.5×3.3	Well-circumscribed	Hypoechoic solid lesion, irregular shape	1-2	Nerve structure is invisible due to massive NMC-DTF	No
5	2/M	sciatic nerve	Hypoechoic, fusiform enlargement	Yes	6.3×4.6×3.6	Well-circumscribed	Hypoechoic solid lesion, irregular shape	1-2	NMC-DTF envelops the proximal adjacent nerve	One
6	4/M	sciatic nerve	Hypoechoic, fusiform enlargement	No	—	—	—	—	—	No
7	3/F	sciatic nerve	Hypoechoic, fusiform enlargement	No	—	—	—	—	—	No

Note: NMC=neuromuscular choristomas; NMC-DTF=neuromuscular choristomas associated desmoid-type formation; CDFI= color Doppler blood flow imaging.

Table 3. Clinical course and follow-up.

Patient	Age/Sex	Location	Surgery before	Transformation of Desmoid-type Formation(DTF)	Treatment process	Pathological finding	Follow-up	
							Tumor recurrence times	Current condition
1	22/F	sciatic nerve	Yes	Yes	Tumor resection (Once)	β -Catenin \boxplus \boxtimes	0	No progression.
2	2/M	sciatic nerve	Yes	Yes	Surgical biopsy of sciatic nerve	β -Catenin \boxplus \boxtimes	0	Progression of motor deficit, limb undergrowth and calf muscles atrophy.
3	6/M	sciatic nerve	Yes	Yes	Tumor resection (Once); chemotherapy (Twice); HIFU (Six times);	β -Catenin \boxplus \boxtimes CTNNB1 p.S45F mutation	Once (At the site of NMC).	Continuous tumor progression lead to above-knee amputation.
4	10/F	brachial plexus	Yes	Yes	Tumor and involved brachial plexus resection, nerve transplantation	β -Catenin \boxplus \boxtimes	0	No progression after nerve transplantation.
5	2/M	sciatic nerve	Yes	Yes	Tumor resection (Three times); radiotherapy (A course)	β -Catenin \boxplus \boxtimes	Twice (At the site of NMC).	No progression after last treatment.
6	4/M	sciatic nerve	No	No	None	—	0	No progression.
7	3/F	sciatic nerve	No	No	None	—	0	No progression.

Notes: HIFU=high intensity focused ultrasound knife; NMC=neuromuscular choristomas.

Figures



Figure 1

Images of patient #1. A 22-year-old female presented with left limb undergrowth (A, B), a cavus foot and the left foot shorter than the right (C). Ultrasound images demonstrated hypoechoic and fusiform enlargement of left sciatic nerve (diameter 2.1cm). The echo intensity of intraneural soft-tissue elements was similar to surrounding skeletal muscle (D). An irregular hypoechoic solid lesion was shown intimately associated with the distal involved sciatic nerve (12.6×3.3cm) (E). MRI demonstrated an abnormal thickening sciatic nerve (1) and a solid mass with irregular borders (Δ) (F). The patient underwent surgery with tumor resection, note the left sciatic nerve revealed marked thickening (1) with desmoid-type fibromatosis (DTF) in branches of the nerve (Δ) (G). Micrograph (H&E) of cross-section affected sciatic nerve showed endoneurial intercalation of mature skeletal muscle fibers among peripheral nerve fascicles and diagnosed neuromuscular choristomas (NMC) (H). Beta-catenin immunohistochemical stain shows both aberrant nuclear staining and cytoplasmic staining in the DTF (I).

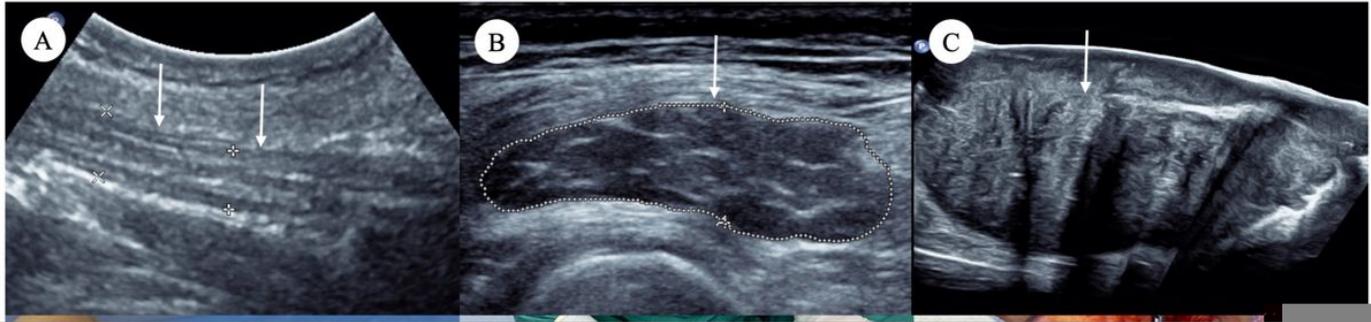


Figure 2

Images of patient #3. A 6-year-old boy with a history of multiple recurrent desmoid-type fibromatosis (DTF) after surgery. Ultrasound images showed hypoechoic and fusiform enlargement of left sciatic nerve in longitudinal section (diameter 1.2 cm) (A) and cross-section (cross-sectional area 2.2 cm²) (B). DTF was shown as an irregular hypoechoic solid lesion at the side of involved nerve (24×17×12 cm) (C). Recurrent DTF developed as a giant mass of left lower limb (D, E). After twice chemotherapy and six times high intensity focused ultrasound knife (HIFU) treatment, the patient underwent amputation surgery, note the left sciatic nerve was marked thickening with skeletal muscle tissue within nerve (F). Micrograph (H&E) of cross-section affected sciatic nerve showed endoneurial intercalation of mature skeletal muscle fibers among peripheral nerve fascicles and diagnosed neuromuscular choristomas (NMC) (G, H). NMC-DTF showed strong Beta-catenin expression in immunohistochemical stain (I) and a CTNNB1 p.S45F mutation was identified.

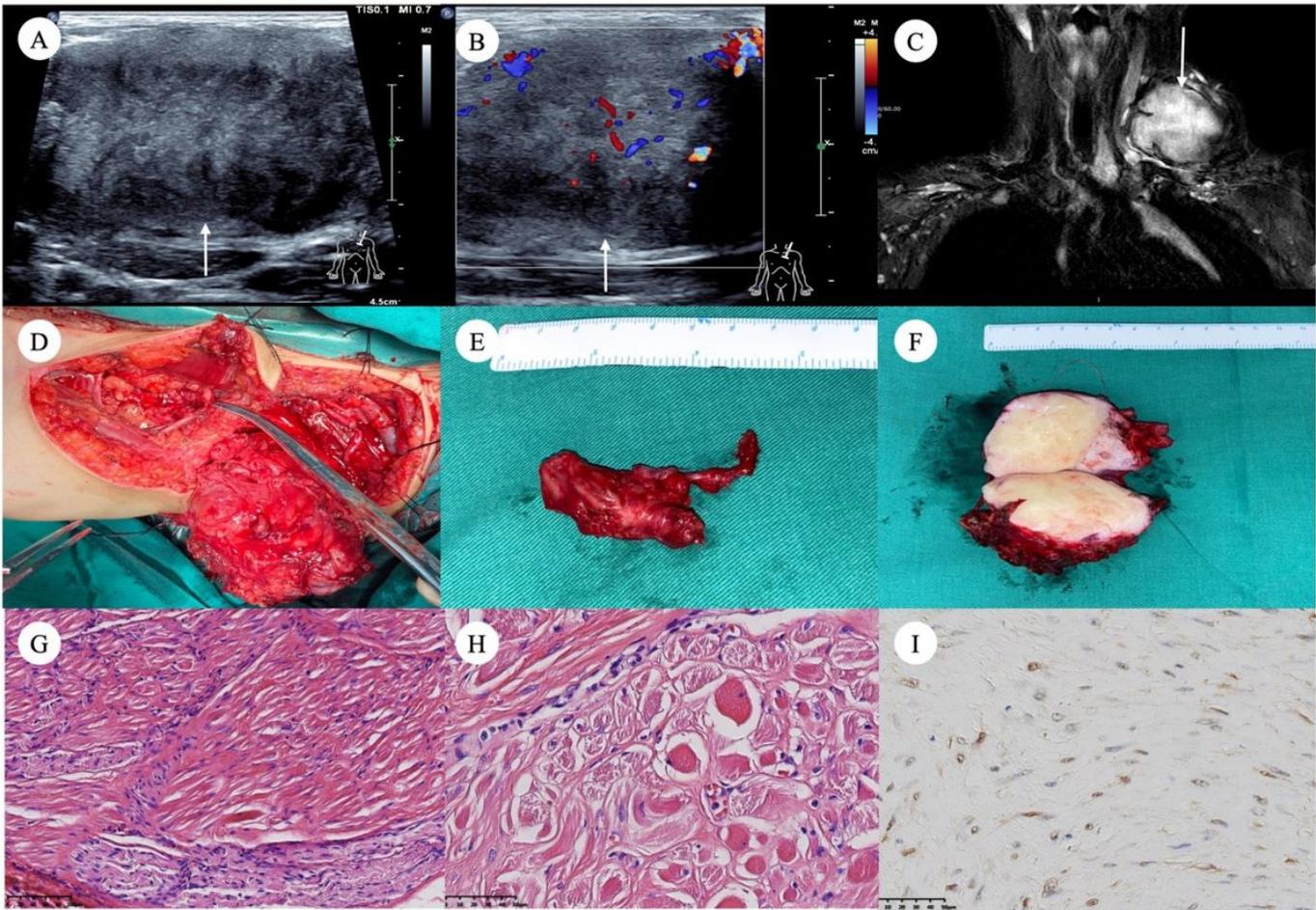


Figure 3

Images of patient #4. A 10-year-old girl with left cervical mass and neuropathic pain. Ultrasound images showed an irregular hypoechoic solid lesion at the course of left brachial plexus (A) with color Doppler flow imaging grade I (B). MRI demonstrated a 5.5×5.5×3.3cm mass with irregular shape consistent with ultrasound images, exhibited the tumor invaded part of the left brachial plexus (C). The patient performed tumor and involved brachial plexus resection and nerve transplantation, note the left brachial plexus was partly surrounded by tumor and partly pressed and narrow (D). Surgical specimen showed thickened C7 nerve root (E) and desmoid-type fibromatosis (DTF) (F). Micrograph (H&E) of cross-section affected sciatic nerve showed endoneurial intercalation of mature skeletal muscle fibers among peripheral nerve fascicles and diagnosed neuromuscular choristomas (NMC) (G, H). Immunohistochemical stain demonstrated strong Beta-catenin expression in NMC-DTF (I).

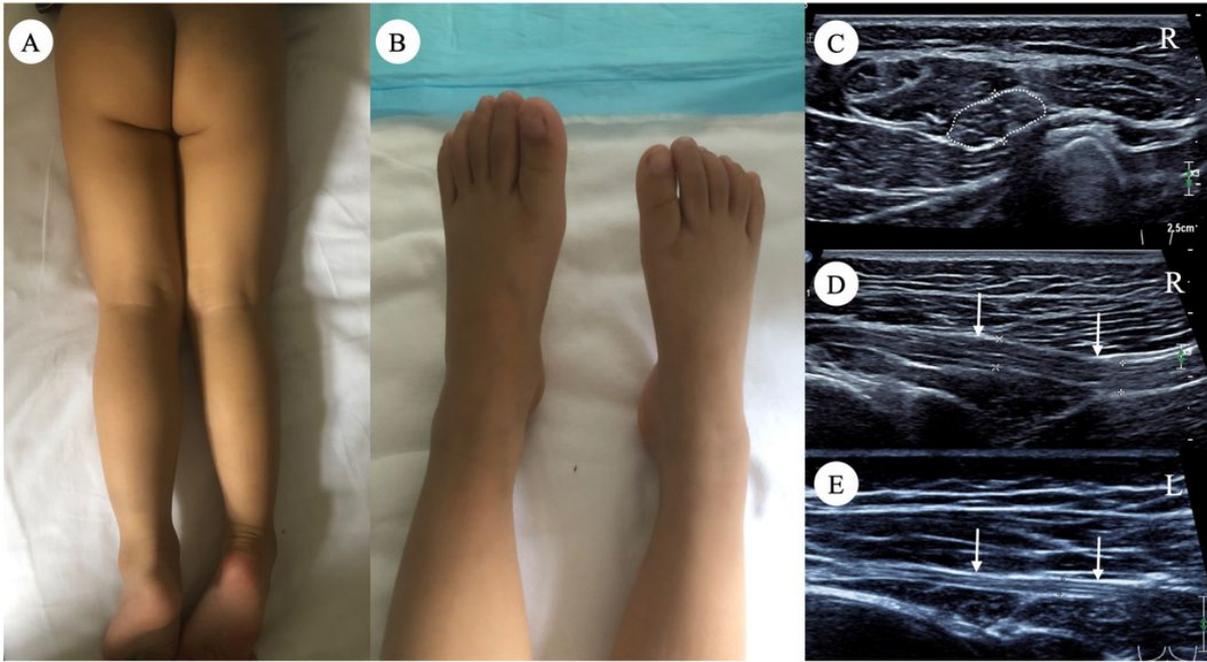


Figure 4

Images of patient #7. A 3-year-old girl with typical clinical manifestations with a neuromuscular choristomas (NMC) of the sciatic nerve, including leg length discrepancy and calf muscles atrophy (A), and the right foot shorter than the left (B). Ultrasound imaging demonstrated that the right sciatic nerve was hypoechoic and fusiform enlarged with prominent soft-tissue elements, echo intensity comparable to skeletal muscle. The cross-sectional area of the nerve was 0.68cm^2 (C) and diameter was 0.47cm in longitudinal section (D). Compared with the other side, the size and echo intensity were normal in the left sciatic nerve (diameter 0.21cm , cross-sectional area 0.23cm^2) (E). No progression of NMC or neuromuscular choristomas associated desmoid-type fibromatosis (NMC-DTF) was found during 8-month follow-up.

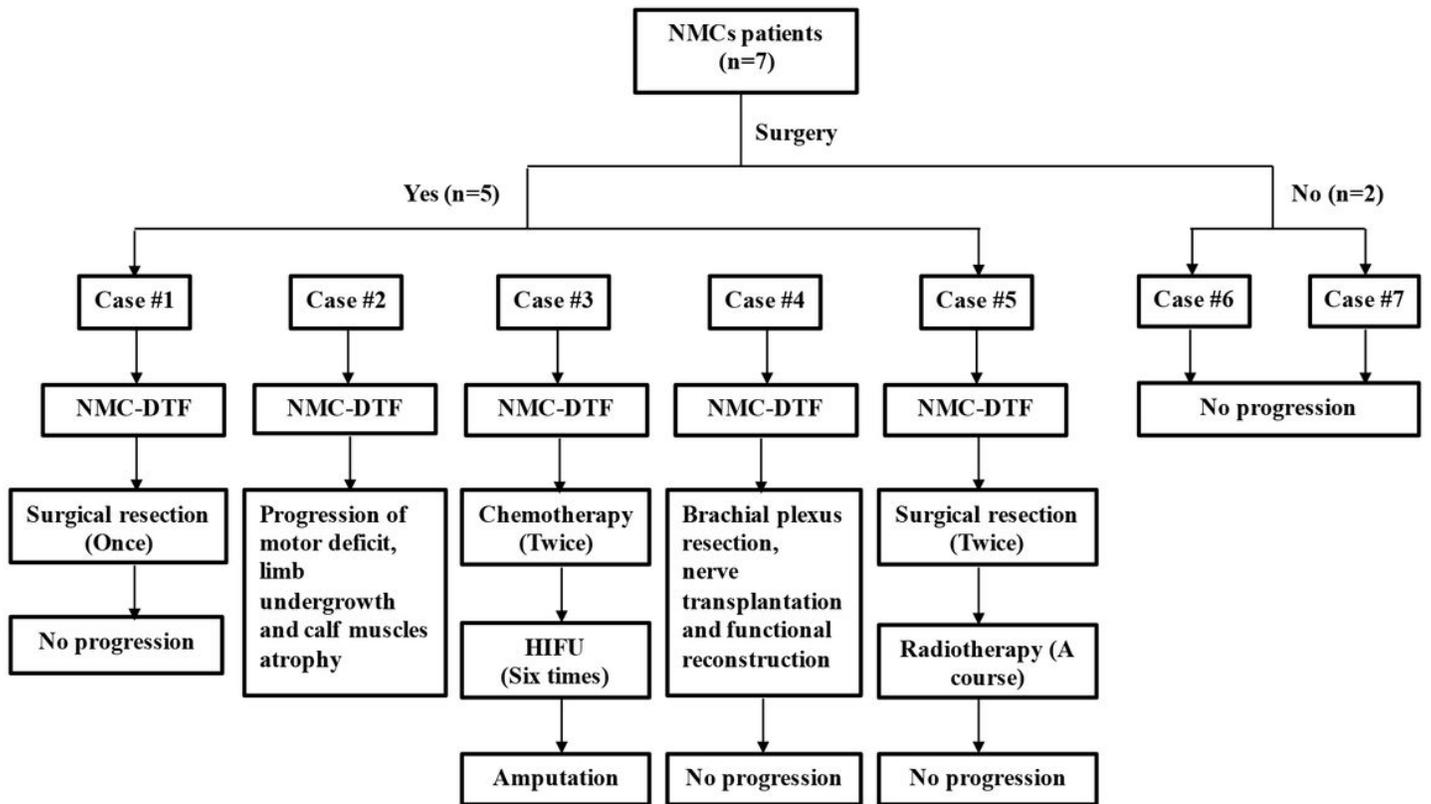


Figure 5

Flow chart of treatment process and follow-up in seven patients.