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Non-Sedated Rapid Volumetric Proton Density MRI Predicts Neonatal Brachial Plexus Birth Palsy Functional Outcome

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ABSTRACT

BACKGROUND AND PURPOSE: The current prognostic biomarker of functional outcome in brachial plexus birth palsy is serial clinical examination throughout the first 6 months of age. This can delay surgical treatment and prolong parental anxiety in neonates who will recover spontaneously. A potentially superior biomarker is a volumetric proton density MRI performed at clinical presentation and within the first 12 weeks of life, providing a high spatial and contrast resolution examination in 4 minutes.

METHODS: Nine neonates ranging in age from 4 to 9 weeks who presented with brachial plexus birth palsy were enrolled. All subjects underwent non-sedated 3 Tesla MRI with Cube Proton Density MRI sequence at the same time as their initial clinical visit. Serial clinical examinations were conducted at routine 4 week intervals and the functional performance scores were recorded. MRI findings were divided into pre-ganglionic and post-ganglionic injuries and a radiological scoring system (Shriners Radiological Score) was developed for this study.

RESULTS: Proton Density MRI was able to differentiate between pre-ganglionic and post-ganglionic injuries. Radiological scores (Shriners Radiological Score) correlated better with functional performance at 6 months of age ($P = .022$) than the initial clinical examinations (Active Movement Scale $P = .213$ and Toronto $P = .320$).

CONCLUSIONS: Rapid non-sedated volumetric Cube Proton Density MRI protocol performed at initial clinical presentation can accurately grade severity of brachial plexus birth palsy injury and predict functional performance at 6 months of age.

Keywords: Brachial plexus, birth palsy, magnetic resonance imaging.

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Introduction

Brachial plexus birth palsy (BPBP), flaccid paralysis of the upper extremity related to birth trauma, results from downward traction of the shoulder girdle during delivery.[1–3] The severity of injury varies widely, and while 80–90% of infants experience complete recovery or mild disability, 10–20% will not recover significant function to the affected extremity.[1,4–6] Distinguishing these 2 groups at initial presentation is often not possible, delaying prognosis and surgical intervention for months.[7,8] While imaging has played only a minor role in assessment of these infants in the past, advances in MRI have made visualization of these damaged nerves possible and may be a method to direct earlier intervention.[9–16]

On a microscopic level, 3 different types of nerve injury are seen with BPBP.[15] They range from complete avulsion of the nerve roots within the spinal canal to a mild stretching injury of the nerves in the plexus (Fig 1).[15,17] More severe injuries require close clinical follow-up and possible reconstructive surgery, while milder injuries can recover with conservative treatment.[5,6,17,18] Clinical scoring systems such as the Active Movement Scale (AMS) and Toronto scores are the current gold standards to determine patient's functional mobility. However, determining long-term functional outcome requires 3 to 6 months of serial examination (Table 1).[17,19,20] There is a critical need for a noninvasive method to accurately determine the extent of BPBP injury and thereby the patient's prognosis earlier than the current standard of serial clinical examination.

Currently used imaging techniques such as CT myelography and heavily weighted T2 MRI sequences are limited because they cannot reliably identify post-ganglionic injuries due to poor soft tissue contrast.[9–11] CT myelography is further limited by the invasiveness of the procedure which requires a lumbar puncture, general anesthesia, and ionizing radiation.[10,13,21,22] Until now, MRI has proven to be a non-invasive alternative to CT myelography, but long scan times, sedation requirements, and similar difficulty identifying post-ganglionic injuries limit its utility.[9,15] By shortening the commercially available proton density (PD) cube volumetric sequence on a General Electric (Waukesha, WI) scanner into a 3.5 minute acquisition, imaging can be accomplished on a non-sedated swaddled neonate while maintaining high soft tissue contrast and spatial resolution. The purpose of our study is to compare this MR imaging technique performed at initial clinical presentation with established serial BPBP clinical scoring systems to assess the ability of MRI

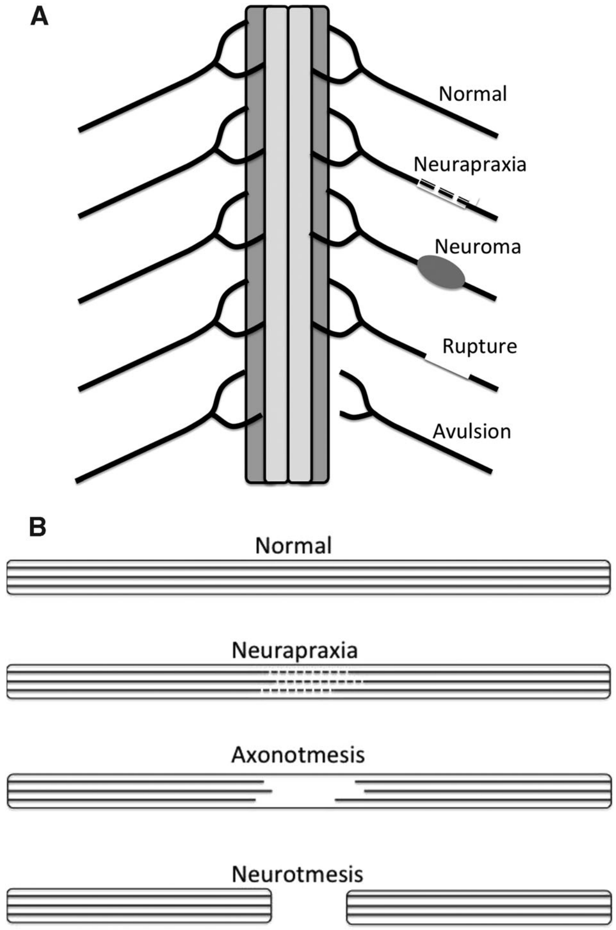

Fig 1. Spectrum of brachial plexus birth palsy injuries. Figure A demonstrates different types of brachial plexus birth palsy injuries from the mildest neurapraxia (stretch injury), to more severe post-ganglionic nerve rupture with and without neuroma formation and pre-ganglionic nerve root avulsion. Figure B demonstrates the different types nerve ruptures from mildest nerve stretching (neurapraxia) to axonal disruption (axonotmesis) to entire nerve disruption (neurotmesis).

to determine severity of BPBP injuries and to predict patients' functional outcome.

Methods

Patient Enrollment

After obtaining Institutional Review Board approval, infants with BPBP under the age of 12 weeks who presented to the BPBP Clinic were eligible for enrollment. Patients were enrolled (February 2014 through January 2015) after obtaining parental consent at their initial clinical visit at the BPBP Clinic. Infants who had concomitant birth injuries (ie, clavicle, rib and humerus fractures or Horner's syndrome, sympathetic chain injury and facial nerve palsies) that would make swaddling and imaging painful for them were excluded. The upper age limit of 12 weeks was set to coincide with the age many infants begin to resist swaddling. Subjects were excluded after enrollment if they were unable to complete the MRI scan due to excessive movement. All subjects were evaluated with routine clinical examinations up to 5–6 months of age, at which time the necessity of surgery was determined by the orthopedic team.

Table 1. Clinical Grading Systems

Active Movement Scale (AMS)	
Grading System	
Gravity Eliminated	***Score***
No Contraction	0
Contraction, no motion	1
<50% motion	2
>50% motion	3
Full motion	4
Against Gravity	***Score***
<50% motion	5
>50% motion	6
Full motion	7

Toronto Score Grading System		
(All movement are against gravity)		
Observation	***Clinical Grade***	***Numerical Score***
No joint movement	0	0
–Flicker of movement	0+	.3
–Less than 50% range	1−	.6
50% range of movement	1	1.0
–More than 50% range	2−	1.6
Full range of movement	2	2.0

Grading scales used for the Active Movement Scale (AMS) and Toronto scores.

Clinical Data

Patients were evaluated for birth weight, gestational age, other injuries at birth (rib, clavicle, and/or humerus fractures), the presence of Horner's syndrome, and diaphragmatic paralysis. AMS for elbow flexion (0 being the most severe and 7 being normal) and Toronto (a selected subset of AMS, 0 being the most severe and 10 being normal) scores were determined at the first BPBP clinical visit prior to MRI. Patients were followed with serial clinical examinations, receiving AMS and Toronto scores at each 4-week interval follow-up visit to determine whether their functional status was improving, worsening, or unchanged. A positive functional arm mobility outcome was defined as improvement in arm mobility (increase in both AMS and Toronto scores at 6 months of age) or maintenance of good arm mobility (AMS $\geq$ 5 or Toronto $\geq$ 8 at 6 months of age).[17,20] A negative functional arm mobility outcome was defined as deterioration in arm mobility (decrease in both AMS and Toronto scores at 6 months of age) or persistent poor arm mobility (AMS $\leq$ 2 or Toronto $\leq$ 4 at 6 months of age).[17,20] If the patients needed surgery, their pre-operative AMS and Toronto scores were recorded, usually occurring at 5 months of age.

MRI Imaging Protocol and Interpretation

Patients underwent non-sedated MRI evaluation within 2 days of their initial clinical visit. The MRI imaging protocol is comprised of a 3-plane localizer and a volumetric PD Cube coronal sequence oriented parallel to the lower cervical spine and extended anteriorly to include the brachial plexus. MRI parameters include slice thickness .8 mm, field of view 17 cm, matrix size 224 by 224, time to relaxation 1400, time to echo 75, flip angle 90, and number of excitations 3. These sequences were 1 and 3.5 minutes in length, respectively, for a total scan time of 4.5 minutes. All MRIs were performed on the same 3-Tesla

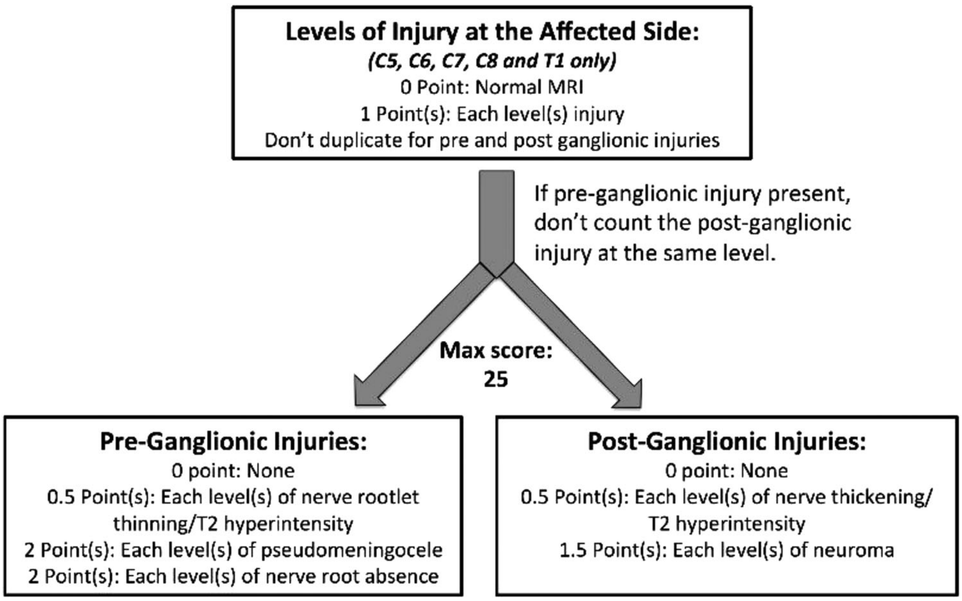

Fig 2. Algorithm for the Shriners Radiological Score (SRS).

General Electric MRI scanner (Waukesha, WI). No anesthesia was required on any of the subjects. In order to decrease patient movement and to calm the infants within the MRI scanner, a swaddling apparatus (Med-Vac^{TM} Infant Immobilizer by CFI Medical, Fenton, MI) was employed, with patient's arms positioned to the side and some limitation of neck rotation.[23]

MR images were reviewed independently by 3 CAQ board certified neuroradiologists for intrathecal pre-ganglionic injuries (pseudomeningoceles with or without nerve rootlet avulsion, or nerve root thinning with T2 hyperintensity) and extra-foraminal post-ganglionic injuries (brachial plexus nerve thickening with T2 hyperintensity with or without neuroma). A radiological scoring system (Shriners Radiological Score [SRS]) was developed to grade the severity of BPBP injuries with an emphasis on pre-ganglionic injuries, specifically absent nerve root and pseudomeningocele (Fig 2). SRS is ascending in severity with 0 being normal and the maximal score of 25 being the most severe.

Data Analysis

Radiological scores (SRS) derived from MRI imaging findings were compared among the 3 reviewers for reliability using Interclass Correlation Coefficient (ICC) analysis. Unpaired *t*-tests were used to compare SRS, initial AMS, and Toronto scores between the positive and negative functional arm mobility outcome groups. Furthermore, imaging findings of pre- and post-ganglionic patterns were then compared with intra-operative findings if infants needed surgical intervention.

Results

A total of 16 subjects, from February 2014 through January 2015, with initial appointments at our BPBP clinic under 12 weeks of age were considered for enrollment, and 13 agreed to participate. Four infants were not able to complete the MRI scan due to excessive motion. The first infant, age 5 weeks, was enrolled prior to our purchase of the MedVac Immobilizer and was unable to complete the MRI protocol due to motion.[23] By the time we received the infant positioner, she was older than 12 weeks, so we were unable to re-image her. The other 3 infants were at the upper end of our age range (8, 11, and 12 weeks) and moved too much during the examination, despite the infant immobilizer, to capture useable images. We considered those infants with entirely unusable MRI scans as withdrawn from the study as we were not able to compare their clinical examinations to MRI findings. This left a total of 9 subjects with usable data.

Study subjects were 4 boys and 5 girls, with an average age of 5 weeks at enrollment (range 3 to 9 weeks). The left side was injured in 5 subjects. The average initial enrollment Toronto score (0 being the most severe and 10 being normal) at presentation was 4.4 (range 0 to 8.2). The average initial enrollment AMS score for the elbow flexion (0 being the most severe and 7 being normal) was 2 (range 0 to 7) (Table 2). All subjects were scheduled for follow-up every 4 weeks from the date of enrollment until 6 months of age. Four of 9 infants in this study had negative functional arm mobility outcome at 6 months and the other 5 had positive functional arm mobility outcome. The same 4 negative functional outcome infants in this study ultimately required microsurgery.[17,19]

The PD Cube MRI sequence provided excellent spatial resolution (.8×.8×.8 mm voxel size) with enough soft tissue contrast resolution to differentiate between pre-ganglionic injuries (pseudomeningoceles with or without nerve rootlet avulsion and nerve root thinning), post-ganglionic injuries (neuromas and nerve root thickening), or intact nerve roots (Figs 3 and 4). The average SRS was 7.3 out of a possible 25 points (ranged from 0 to 19), with 0 representing no visible injury and 25 representing complete nerve root avulsions with pseudomeningoceles (pre-ganglionic injuries) at all 5 nerve roots of the brachial plexus (Table 3).

There was near complete agreement between the 3 interpreting neuroradiologists, with the Interclass Correlation Coefficient of the 3 calculated SRS as .957.

Of the infants who had positive functional arm mobility outcome at 6 months of age, SRS ranged from 0 to 8, while the

Table 2. Patients' Initial Radiological and Clinical Scores versus Functional Outcome

Patient ID	Age at Enrollment (weeks)	SRS	AMS for Elbow Flexion at Enrollment (0-7 weeks)	AMS for Elbow Flexion at 6 Months of Age (or at Preop*)	Functional Outcome at 6 Months of Age (Positive/ Negative)
2	4	6.5	2	2*	Negative
3	4	9.5	2	2*	Negative
4	7	18	0	0*	Negative
5	7	3	2	4	Positive
6	5	0	7	7	Positive
7	8	14	0	2*	Negative
9	4	0	2	6	Positive
10	4	6.5	2	5	Positive
13	9	8	1	6	Positive

A

Patient ID	Age at Enrollment (weeks)	SRS	Toronto Score at Enrollment (0-7 weeks)	Toronto Score at 6 Months of Age (or at Preop*)	Functional Outcome at 6 Months of Age (Positive/ Negative)
2	4	6.5	6.4	7.5*	Negative
3	4	9.5	6.3	6.6*	Negative
4	7	18	0	.3*	Negative
5	7	3	1.2	6.5	Positive
6	5	0	5.9	10	Positive
7	8	14	0	.6*	Negative
9	4	0	8.2	9.6	Positive
10	4	6.5	6.9	9.3	Positive
13	9	8	4.9	9.6	Positive

B

Comparison of Shriners Radiological Score (SRS) to Active Movement Scale (AMS) for elbow flexion (A), and Toronto scores (B) for infants in the study. Non-consecutive patient ID numbers are due to exclusion of those infants who did not tolerate the MRI. Positive functional arm mobility outcome is determined by improvement in arm mobility (increase in both AMS and Toronto scores at 6 months of age) or maintenance of good arm mobility (AMS ≥ 5 or Toronto ≥ 8 at 6 months of age). Negative functional arm mobility outcome is deterioration in arm mobility (decrease in both AMS and Toronto scores at 6 months of age) or persistent poor arm mobility (AMS ≤ 2 or Toronto ≤ 4 at 6 months of age).* If the patients needed surgery, their pre-operative AMS for elbow flexion and Toronto scores were reported, usually occurring at 5 months of age.

scores for infants who had negative functional arm mobility outcome ranged from 6.5 to 18 (Tables 2 and 3). The difference in SRS between the 2 groups was statistically significant ($P = .022$). In contradistinction, there was no significant difference in initial AMS elbow flexion and Toronto score between 2 functional outcome groups ($P = .213$ and .320, respectively).

Discussion

In this study, we developed a rapid non-sedation MRI protocol with high spatial resolution and soft tissue contrast, which can reliably determine the level and extent of BPBP injury with high inter-rater reproducibility. A scoring system based on the MRI findings (SRS) at initial clinical presentation was able to differentiate those infants who would recover arm mobility function spontaneously versus those who would not ($P = .022$), in contrast to initial clinical examinations: AMS ($P = .213$) and Toronto Score ($P = .320$) (Table 2).

Our findings indicate that the severity of both pre-ganglionic (pseudomeningoceles with or without nerve rootlet avulsion) and post-ganglionic (brachial plexus trunk level nerve rupture with or without neuroma formation) BPBP injury can be accurately assessed with MRI earlier in the life of injured infants than is currently feasible with clinical examinations. The benefits of earlier diagnosis are 3-fold. If poor functional outcome is to be expected, infants may benefit from earlier surgical reconstruction if needed and may lead to better surgical results.[5,6,8,17,19] Alternatively, if spontaneous functional recovery is to be expected, families may be spared weeks to months of worry. Lastly, for those requiring surgery, early MR imaging can provide operative guidance as pre- and post-ganglionic injuries require different operative approaches (rerouting vs. repair, respectively), and thus may reduce operative time and enhance effectiveness of surgical reconstruction.[14,15]

The imaging method we have developed and tested is, to the best of our knowledge, the first of its kind to be used in the assessment of BPBP. Prior studies have evaluated the utility of MRI imaging via a retrospective approach where patients who went to surgery had their intra-operative findings compared to imaging findings.[14–16] Imaging was only performed on patients who did not demonstrate good clinical recovery.[9,10] As such, the ability of MRI to predict the functional arm mobility outcome of patients has yet to be tested.

The MRI SRS is promising, but it is not a perfect biomarker in differentiating the spontaneous functional recovery and persistent functional deficit groups. As seen in the patient #2 and #10, both presented with an AMS of 2 out of 7 for elbow flexion, the same SRS score of 6.5, and the same MRI imaging findings (right C5 neuroma, right C6 neuroma, and right C7 trunk level nerve thickening) (Fig 4). However, Patient #2 never recovered elbow flexion (AMS = 2 at 5 months), while Patient #10 regained most elbow flexion (AMS = 5 at 6 months). This example illustrates the true challenges of non-invasive imaging evaluation in BPBP. The ideal test would need to provide a microscopic assessment of the perineurium and epineurium integrity, thereby differentiating between axonotmesis and

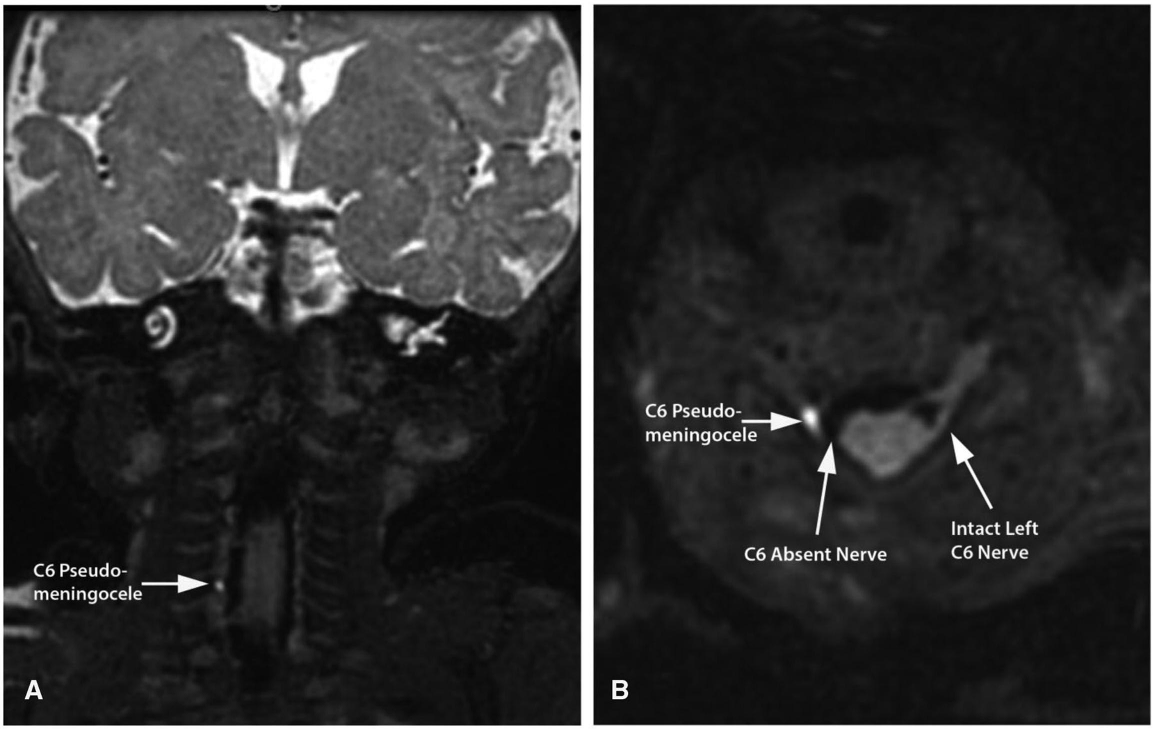

Fig 3. Coronal (A) and axial (B) PD Cube MRI images in a 9-week-old infant demonstrate right C6 nerve pre-ganglionic injury with a pseudomeningocele and absent nerve root. The intact left C6 nerve root is indicated in comparison.

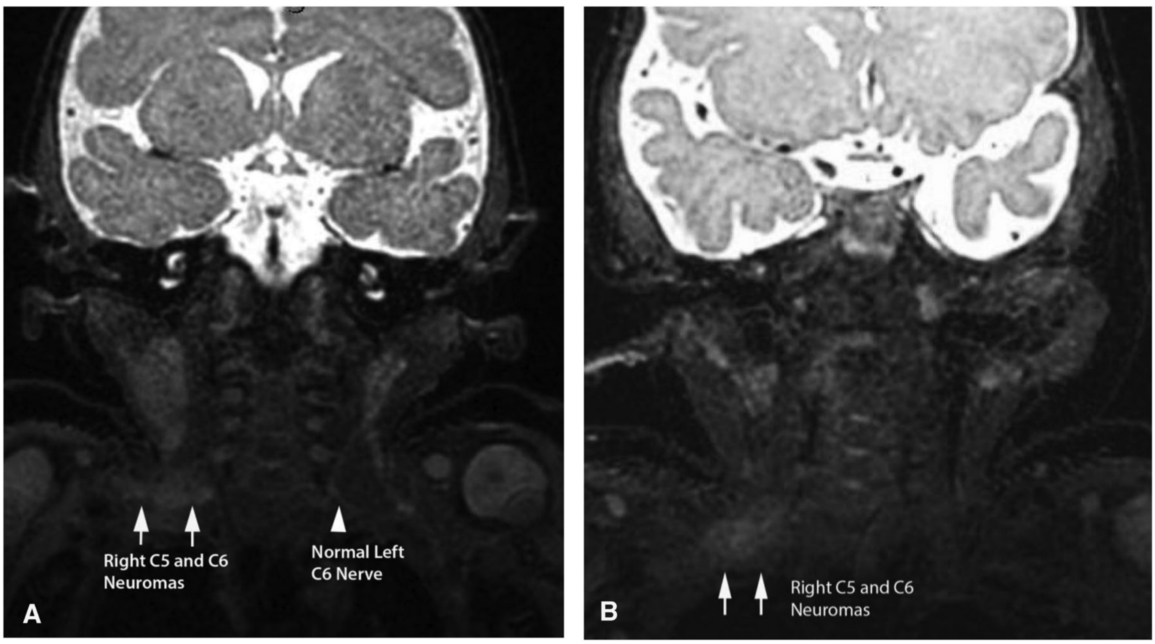

Fig 4. Coronal PD Cube image in Patient #2 (A) demonstrates post-ganglionic injuries: right C5 and C6 nerve ruptures and neuromas, with normal left C6 nerve as comparison. Coronal PD Cube image in Patient #10 (B) demonstrates similar post-ganglionic injuries: right C5 and C6 nerve ruptures and neuromas.

neurotmesis (Fig 1). At this time, no imaging or clinical tests are able to accomplish this. Clinical follow-up examinations only to 6 months of age is a limitation of the study, but clinical visits are ongoing and the data will be reported in future publications. Nonetheless, the majority of observation BPBP studies suggest that most infants who will make a spontaneous recovery do so by 6 months of age, and those infants who do not by 6 months of age may need surgical evaluation and possible surgical brachial plexus reconstruction.[2,3,6,17] Since all 4 negative outcome patients required surgical reconstruction, the SRS could potentially serve as a biomarker for early surgical intervention. A possible SRS threshold for surgery is in the range

Table 3. Independent Reviewers' Scores, Specific Imaging, and Surgical Findings

Patient ID	Findings on MRI	SRS-1	SRS-2	SRS-3	Findings at Surgery Nerve Graft (Y/N) Number and Type of Nerve Grafts
2	Right C5, Neuroma Right C6 Neuroma Right C7 NT Thickening	6.5	7.5	6.5	Right C5, C6 Avulsion No
3	Right C6 PM (+NR) Right C7 PM (−NR) Right C8 NR Thinning	9.5	11.5	8	Right C5, C6 Rupture Yes 8 Sural Nerve
4	Left C5 NR Thinning Left C6 PM (-NR) Left C7 PM (-NR) Left C8 PM (-NR) Left T1 NR Thinning Left C5 NT Thickening	18	19.5	19	Right C5, C7, C8, T1 Avulsion Right C6 Rupture Yes 3 Sural Nerve
5	Left C8 NR Thinning Left T1 NR Thinning Left T1 NT Thickening	3	3	6	Surgery Not Indicated
7	Left C7 PM (-NR) Left C8 PM (-NR) Left T1 NR Thinning Left C6 Neuroma	14	13	11	Left C7, C8 Avulsion Left C5, C6 Rupture Yes 7 Sural Nerve
6	Normal	0	0	1.5	Surgery Not Indicated
9	Normal	0	0	0	Surgery Not Indicated
10	Right C5 Neuroma Right C6 Neuroma Right C7 NT Thickening	6.5	7.5	4	Surgery Not Indicated
13	Right C6 PM (-NR) Right C5 NT Thickening Right C7 NT Thickening	8	8	8	Surgery Not Indicated

Comparing imaging, Shriners Radiological Score (SRS) scores (for all 3 reviewers), surgical findings, and surgical nerve grafts used for those infants who underwent surgery. MRI findings of pre-ganglionic injuries include pseudomeningocele (PM) with presence or absence of nerve roots (+ NR/- NR) and nerve root thinning (NR Thinning). MRI findings of post-ganglionic injuries include neuroma and nerve trunk level thickening (NT Thickening).

of 6.5-8, which is the overlap between the negative and positive functional outcome groups. Of course, additional studies are required to refine and confirm these findings.

Additional limitations of this study include a small cohort despite statistical significance, as well as possible selection bias with exclusion of patients with concomitant birth injuries. While these limitations were selected for our pilot study to obtain a more uniform patient population, further study with large and diverse patient populations will be needed to confirm the findings in this paper. Future directions of this study also may include additional volumetric MRI sequences[24] and diffusion tensor imaging (DTI), which characterizes magnitude, anisotropy, and orientation of axonal fiber tracks and thus axonal integrity.[25,26] DTI may characterize the microstructural changes within injured neural bodies and axons, and is a promising tool for future BPBP investigations.

Conclusion

Rapid, non-sedated, non-contrast, volumetric PD Cube MRI sequence with high spatial resolution and soft tissue contrast can accurate assess both pre- and post-ganglionic BPBP injuries. This MRI protocol, performed at clinical presentation, can distinguish between infants who will make significant functional improvements from those who will not regain any arm mobility. The MRI scoring system developed (SRS) reliably distinguished between these 2 groups and correlated better with the 6-month clinical examination scores (AMS and Toronto) than the initial clinical examination. However, a larger multi-center study is required to confirm that this imaging protocol can be a rapid non-invasive biomarker in future clinic care of BPBP patients.

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