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ORIGINAL ARTICLE

Brain plasticity in neonatal brachial plexus palsies: quantification and comparison with adults' brachial plexus injuries

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Abstract

Purpose To compare two populations of brachial plexus palsies, one neonatal (NBPP) and the other traumatic (NNBPP) who underwent different nerve transfers, using the plasticity grading scale (PGS) for detecting differences in brain plasticity between both groups.

Methods To be included, all patients had to have undergone a nerve transfer as the unique procedure to recover one lost function. The primary outcome was the PGS score. We also assessed patient compliance to rehabilitation using the rehabilitation quality scale (RQS). Statistical analysis of all variables was performed. A $p \leq 0.050$ set as criterion for statistical significance.

Results A total of 153 NNBPP patients and 35 NBPP babies (with 38 nerve transfers) met the inclusion criteria. The mean age at surgery of the NBPP group was 9 months (SD 5.42, range 4 to 23 months). The mean age of NNBPP patients was 22 years (SD 12 years, range 3 to 69). They were operated around sixth months after the trauma. All transfers performed in NBPP patients had a maximum PGS score of 4. This was not the case for the NNBPP population that reached a PGS score of 4 in approximately 20% of the cases. This difference was statistically significant ($p < 0.001$). The RQS was not significantly different between groups.

Conclusion We found that babies with NBPP have a significantly greater capacity for plastic rewiring than adults with NNBPP. The brain in the very young patient can process the changes induced by the peripheral nerve transfer better than in adults.

Keywords Plasticity Grading Scale · Neuroplasticity Score · Neonatal Brachial Plexus Palsy · Brachial Plexus Injury · Nerve Transfer · Brain Plasticity

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Introduction

Neonatal brachial plexus injuries (NBPP) occur during birth due to traction on the nerves running from the neck to the arm. Immediately after birth, patients have motor and sensory deficits of the upper limb. Spontaneously, recovery takes place in around 70% of the babies [1]. In severe cases, functional deficits remain throughout their entire lifespan. Functional improvement can be obtained with reconstructive nerve surgery and/or secondary surgery in a selective group of NBPP patients [2, 3]. Nerve surgery entails reconstruction of spinal roots with autologous nerve grafts, nerve transfers, or a combination of both [2–4]. In a nerve transfer, a normal functioning nerve (donor) is cut and connected to the distal end of a non-functioning, but more important nerve (acceptor). Following a nerve transfer, the control over the reinnervated function is initially by the donor nerve command.

The regain of volitional control, i.e., a functional response following the acceptor nerve command, requires central neural plasticity. This is the inherent capacity of the brain and spinal cord to adapt to changes in external or internal stimuli. Neural plasticity is a process that helps in learning, develop motor skills to execute new tasks, and minimize deficits [5–8]. The capacity of the nervous system for central plastic changes is of great importance because it determines the final functional result of the applied nerve transfer [3, 9].

Recently, we developed the plasticity grading score (PGS) to objectify the level of volitional control after nerve transfer [3]. In adults or children sustaining a traumatic brachial plexus injury after a motorcycle or car accident (NNBPP), independent control over the reinnervated function can be reached. However, in more than three-quarters of the cases complete independence was never attained [3]. For instance, when a phrenic nerve transfer for elbow flexion was done, complete inspiration by firing the phrenic nerve increased the strength of the reinnervated biceps in up to 10% even years after the surgery [10, 11]. We concluded therefore that these lack of complete independence of voluntary control observed between donor and acceptor motor programs were due lo limitations on plasticity observed in the analyzed population, comprised mostly of adult patients. Furthermore, we compared the PGS score of adults with NNBPP and NBPP patients in which one specific nerve transfer was performed, namely, the ulnar or median branches to musculocutaneous nerve transfer. We found that the capacity for plastic changes was much bigger in the infant than in the adult [12]. Whether this difference only accounts for this specific transfer or for nerve transfers in general is still unknown.

Here, instead of comparing both populations analyzing only one transfer, we studied the differences in PGS scores between NBPP and NBPP patients after those different nerve transfers which are most frequently used, namely, the ulnar and or median nerve fascicles to musculocutaneous nerve, spinal accessory nerve to nerves for elbow flexion, spinal accessory to suprascapular nerve, intercostal to musculocutaneous nerve, triceps branches to axillary nerve, and phrenic nerve to nerves for elbow flexion.

Materials and methods

Inclusion criteria

We retrospectively reviewed infants with NBPP and adults with NNBPI for which a nerve transfer was performed. All patients were operated upon consecutively in the Peripheral Nerve Unit within the Department of Neurosurgery, University of Buenos Aires School of Medicine between January 1st, 2002, and December 31st, 2018. To be included in the study, both NBPP and NNBPP had to have undergone an extra or intra-plexal nerve transfer to regain a lost neurological function but not nerve grafting for the same function. Therefore, in all included cases, the specific nerve transfer was the only nerve surgical technique used. The patients who underwent grafting were excluded because if a nerve root was reconstructed with grafts and subsequently a nerve transfer was performed to recover the same or a similar function, it is not possible to determine if the recovery was either due to the root repair or to the nerve transfer.

The primary outcome was the PGS score, ranging from 1 to 4 (Table 1) [3]. Briefly, PGS score 1 represented the lowest independent volitional control, with British Medical research Council (MRC) grade 4 obtained in response to the donor command and MRC grade 0 in response to the acceptor command (minimum brain plasticity), whereas PGS score 4 was no noticeable contraction in response to the donor command and MRC score 4 in response to the acceptor command (maximum brain plasticity). Each muscle reinnervated following the transfer was tested three times in.

We also assessed patient compliance with the rehabilitation therapy using the 4-point rehabilitation quality scale (RQS) [3, 13–15]. An RQS score of 1 represents patients who failed to attend any rehabilitation therapy or attended less than once weekly. Patients who had rehabilitation therapy at a regular center more than once weekly were classified as RQS of 2, and a score of 3 was attained when patients exhibited good adherence to a rehabilitation program at a nonspecialized neuro-rehabilitation center with periodic assessments at a specialized neuro-rehabilitation center.

Table 1 Plasticity grading scale (PGS) after nerve transfer

Grade	Target muscle contraction ↔ motor program activation	MRC of target muscle contraction with donor command	MRC of target muscle contraction with acceptor command
I	Exclusively donor (no plasticity)	M4	M0
II	Via donor and acceptor (poor plasticity)	M2, M3 or M4	M4
III	Subtle via donor, predominantly via acceptor (good plasticity)	M1	M4
IV	Exclusively acceptor (excellent plasticity)	M0	M4

Patients who exhibited good adherence to a rehabilitation program at our specialized institution were assigned an RSQ score of 4 (Table 2).

The exclusion criteria were (1) patients who were lost to follow-up; (2) a clinical final result of the nerve transfer of MRC grade < 4; (3) surgical repair more than 12 months after the trauma; (4) NNBPP patients who had a concurrent brain contusion which might have affected their potential for brain plasticity, or (5) follow-up of less than 12 months. Finally, we studied the influence of the compliance of each patient to the rehabilitation plan (Table 2), the time from trauma to surgery, and the time of follow-up, in order to determine whether these independent factors predict a response in the PGS score.

The study was performed in full accordance with the Declaration of Helsinki II and our institution's ethics committee. All eligible patients — or responsible parents in children or NNBPP cases) — were asked to participate in our study protocol, which included a throughout clinical examination. Written informed consent was obtained from each patient prior to study participation. Patient demographic characteristics — like gender, age, time from trauma to surgery, and the duration of follow-up — were recorded at the time of assessment.

Surgical strategies and techniques

General descriptions of the brachial plexus surgery and also of our rehabilitation program have recently been published [15–17]. All nerve transfers included a complete or a partial nerve section of the donor nerve and a direct coaptation with the recipient nerve. Nerve transfers only were used when proximal roots for grafting were unavailable as assessed by preoperative MRI and intraoperative inspection. Post-operative evaluations were performed every 6 months by at least two of the authors.

Post-operative clinical evaluation

Post-operative evaluations were performed every 6 months on a regular basis by at least two of the authors to reduce ascertainment bias. After a general clinical evaluation, we determined the PGS score. Post-operative evaluations were performed every 6 months by at least two of the authors.

Statistical analysis

Continuous variables (age at surgery in months, time of follow-up in months, compliance to rehabilitation scale, and plasticity scale) were summarized as means with standard deviations (SD) and minimum to maximum ranges and then tested for normality of distribution using the Shapiro–Wilk's test. Since all four continuous variables were non-normally distributed and were being compared between subject groups (NBPP versus NNBPP), Kruskal–Wallis one-way analysis of variance (KW-ANOVA) was used to compare medians and distributions. Distributions for both PGS scores and compliance were further compared using Pearson $\chi2$ analysis or Fisher's exact test, as indicated. Within each subject group, the degree and significance of correlations between the four continuous variables were calculated using Pearson correlation coefficients, with r values < 0.30 considered weak, from 0.30 to 0.69 moderate, and ≥ 0.70 strong correlations. To identify predictors of the final neuroplasticity score, simple linear regression analysis was performed with the four independent variables — subject group, time to surgery, length of follow-up, and compliance score entered by forward entry. All tests were two-tailed, with $p \leq 0.050$ set as the a priori criterion for statistical significance.

Results

Comparing two series

A total of 153 NNBPP patients and 35 NBPP babies met the inclusion criteria. The demographic characteristics of the NBPP and NNBPP patients are shown in Table 3. The mean age at surgery of the NBPP group was 9 months (SD 5.42, range 4 to 23 months), and approximately half of them were male. The duration of follow-up and the compliance with the rehabilitation scale were not very different than NNBPP patients (Table 3). The mean age of NNBPP patients was 22 years (SD 12 years, range 3 to 69). They were operated around the sixth months after the trauma and more than 90% were male. In Tables 4 and 5, a description of the surgical techniques used in each group (NBPP and NNBPP) is described, as well as the number of individuals sustaining each technique. All NNBPP patients underwent one nerve

Table 2 The rehabilitation quality scale (RQS) used to quantify adherence to and the quality of a patient's post-operative rehabilitation program

Score description
1 No rehabilitation therapy at all or less than once a week
2 Rehabilitation therapy more than once per week, but not at a specialized neuro-rehabilitation center
3 Good adherence with the entire rehabilitation program, but not at a specialized neuro-rehabilitation center; periodically assessed at a specialized neuro-rehabilitation center
4 Patient adheres perfectly to the entire rehabilitation program at a specialized neuro-rehabilitation center

Table 3 Demographic characteristics of patients of the sample

Patient group	Variable	Mean	SD	Range
NNBPP	Age (years)	28.22	12.41	3–69
($N=153$)	% males	92.2%		
	Time to surgery (months)	6.37	3.03	1–19
	Duration of follow-up (months)	53.93	35.13	12–182
	Compliance score	3.04	0.76	2–4
	Plasticity score	3.05	0.65	1–4
NBPP	Age (months)	9	5.42	4–23
($N=38$)	% males	47.4%		
	Time to surgery (months)	9.18	5.06	3–23
	Duration of follow-up (months)	44.39	31.58	12–132
	Compliance score	2.76	0.97	1–4
	Plasticity score	4.00	0.00	4–4

transfer, whereas in the NBPP group, some had two transfers for different functions resulting in a total of 38 nerve transfers.

All transfers performed in NBPP patients had a PGS score of 4, while all nerve transfers in NBPP group scored the maximum. This was not the case for the NNBPP population that reached a PGS score of 4 in less than one quarter of the cases (Fig. 1).

The difference in PGS scores of infants with NBPP and patients with NNBPP was statistically significant ($p<0.001$, Table 6). Furthermore, time to surgery differed significantly between both groups ($p<0.001$, Table 3).

The PGS score of the total group of NNBPP patients was 3.05. The PGS score in this group was better following an intraplexal transfer (triceps to axillary PGS score 3.15, ulnar and/or median fascicle to musculocutaneous PGS score 3.27) than following an extra plexal transfer (phrenic nerve for elbow flexion PGS score 2.57, spinal accessory nerve for elbow flexion PGS score 2.95) (Table 7). No statistical difference in the PGS scores of the different nerve transfer techniques was found.

The compliance to rehabilitation measured employing the RQS was not significantly (Table 6) different when comparing NBPP and NNBPP groups. (2.76 versus 3.04, respectively, Table 3).

Table 4 Nerve transfers employed in NNBPP ($n=153$) patients

Nerve transfer	Number	Mean plasticity grading scale
Phrenic nerve for elbow flexion	44	2.57
Spinal accessory nerve for elbow flexion	40	2.95
Oberlin (double or single)	44	3.27
Triceps to axillary	25	3.15
Total group	153	3.05

Discussion

Differences in plasticity between NBPP babies and NNBPP patients

Nerve transfers are frequently used to reanimate function lost due to root avulsions both in NBPP [2–4, 13, 18–21, 22]. Functional outcome following brachial plexus repair is in part determined by the level of volitional control over the reinnervated muscle. This is not so obvious after a nerve transfer. After all, brain programs for control of function of the donor nerve are different from those of the acceptor nerve. The recovery of volitional control depends on the degree of plasticity. The degree of plasticity can be expressed using the PGS [3]. Similar nerve transfers are used in both NBPP and NNBPP injuries. It is important to know in both groups what can be expected with regard to regaining volitional control after the operation. The fact that the surgical transfer technique is similar in both groups does not automatically imply that the level of cerebral control after reinnervation also becomes the same. Therefore, we investigated whether there is a difference in the level of volitional control achieved after nerve transfers in NBPP in babies as compared to NNBPP in adults. The main finding of this study was that there was a statistically significant difference between the PGS scores of babies with NBPP and adults with NNBPP. Nerve surgeons should be aware of this difference while informing their patients (Fig. 2).

The mechanisms underlying brain plasticity after a nerve transfer have been extensively studied [6–9, 23–25]. In view of the relatively short time in which the control over the reinnervated muscle shifts from the donor program to the acceptor program and the cortical distance between both programs the mechanism underlying plasticity is the increase of the efficiency of signaling in pre-existing pathways between donor and acceptor programs. This occurs by unmasking of previously silent synaptic connections rather than arborization of dendrites.

It is a well-determined phenomenon that newborns and children in general have a more plastic brain than adults, as plasticity decreases with age [12, 26, 27]. In confirmation of these fact, all babies with NBPP had the maximal PGS score of 4, regardless of the applied nerve transfer. Apparently, the process of rewiring in the motor cortex is going very well at early age when the brain is in a developing stage. Theoretically, this may imply that NBPP patients may potentially be good candidates for the contralateral C7 root transfer for hand or elbow flexion. This transfer is not widely accepted in the nerve surgical community for use in adults patients because of the lack of volitional control. This assumption, however, needs to be studied. Other studies point in the same direction as the current one. NBPP patients with a right palsy usually change their language-dominant hemisphere

Table 5 Nerve transfers ($n = 38$) employed in NBPP patients ($n = 35$)

Nerve transfer	Number	Mean plasticity grading scale
Ulnar fascicle to MCN biceps branch	22	4
SAN to SS	3	4
Spinal accessory nerve for elbow flexion	4	4
ICN to MCN	6	4
Triceps branches to axillary nerve (anterior division)	3	4

from left to right [28] as a result of plastic changes occurring at early stages of development. Similarly, fMRI studies showed that the increased use of the left hand (forced at early ages due to a right NBPP) induces primary and secondary cortical changes — called hand knob — enlargements of the left hand area, similarly to what occurs in natural left-handed dominant [29–32]. Lastly, it has been reported that children below 6 years old that started learning English as a foreign language in Saudi Arabia before they reach 6 years of age learn the language much easier, faster, and mostly as a native language [27].

It has been hypothesized that plastic changes are more successful if the donor and acceptor cortical motor programs are located close rather than with a distance [2, 6, 7, 9, 11, 33]. In babies with NBPP, this difference could not be observed.

In adults with NNBPP, extra-plexual nerve transfers had worse PGS scores when compared to intra-plexual ones, but as described, the differences were not significant.

We found that in a group of patients with NNBPP, a trace of movement related to donor nerve program was present in more than 80% [12]. We interpreted this finding as a limitation of brain plasticity in already developed brains. These findings where present even after more than 10 years [12, 34].

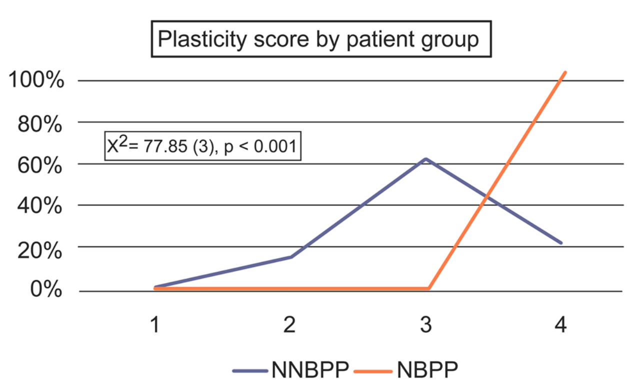

Fig. 1 Distribution of compliance measured with the RQS — NNBPP versus NBPP groups

Demographic results: comparison between NBPP and NNBPP patients

Both groups of patients showed some differences. NBPP patients were in the vast majority male who suffered a motorcycle accident [35], while the sex distribution was similar in NBPP (Table 3). So far, there are no studies that have analyzed potential differences in the capacity for plastic rewiring between male and female.

Additionally, the time between trauma and surgery differed for reasons related to the different managements of each type of trauma. Generally, prolonged denervation is related to worse outcome of reconstruction [36] Therefore, early surgery is frequently advised [4, 5, 13, 33]. However, babies who have a NBPP may recover spontaneously in around 70–80% [37] probably due to the relatively low amount of kinetic energy involved which is exerted over a period of minutes. Thus, unless a severe injury is diagnosed (i.e., a complete palsy with accompanying Horner sign or root avulsions determined by MRI), later surgeries are not uncommon. In addition, late referrals to our center are not uncommon. Notably, the statistically significant difference in interval between trauma and surgery, being longer in babies, did not affected the plasticity after a nerve transfer, a fact that again remarks the elevated plasticity shown by the NBPP group.

The compliance to rehabilitation (as we scored, using RQS) [3, 11–13, 33] showed some differences between groups although they were not statistically significant. Nevertheless, and similarly to what was observed regarding the difference

Table 6 Comparison of NBPP with NBPP patients

	Subject group		Different	Different
Variable	NNBPP	NBPP	means	distributions
Time to surgery	6.37	9.18	$p < 0.001$	$p < 0.001$
Duration of follow-up	53.93	44.39	$p = 0.050$	$p = 0.068$
Compliance score	3.04	2.76	$p = 0.83$	$p = 0.071$
Plasticity grading scale	3.05	4.00	$p < 0.001$	$p < 0.0005$

Table 7 Nerve transfers employed in BPI ($n = 153$) and plasticity score (PGS) achieved

Nerve transfer	Total number of cases	Number of cases achieving grades (in PGS)				
		1	2	3	4	Mean
Phrenic to (ADUT, LC, MCN, BB)	44	0	11	33	0	2.57
Spinal accessory to MCN	40	1	4	34	1	2.95
Median and/or ulnar fascicle to MCN	44	0	4	20	20	3.27
Triceps to axillary	25	0	2	16	7	3.15

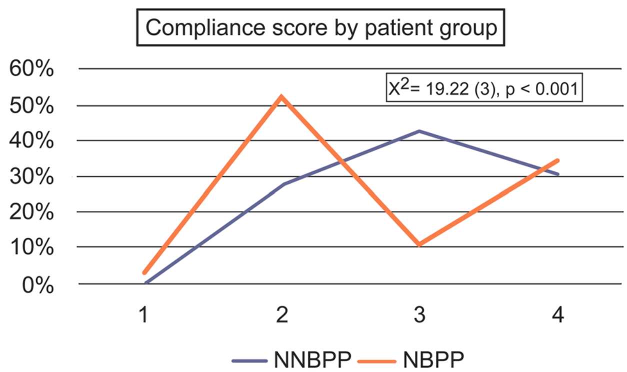

Fig. 2 Distribution of plasticity measured in PGS — NNBPP versus NBPP groups

in timing for surgery, the aforementioned difference in compliance to the rehabilitation did not imply a worst result in terms of plasticity, probably being the latter stronger than the former.

Limitations and originality of our study

This study was retrospective of nature and included a relatively limited number of patients, especially those with NBPP. We included different types of nerve transfers and grouped the PGS scores. The differences in nerve transfers were not evenly distributed in both groups. Differences in plasticity per type of transfer may exist, which may affect the outcome. Noteworthy, this is the first report of a comparison between adults and babies regarding brain plasticity measured using the PGS that included different types of nerve transfers for brachial plexus injuries.

Conclusions

Plastic changes in the brain determine volitional control over a reinnervated muscle following a nerve transfer. We found that babies with NBPP have a significantly greater capacity for plastic rewiring than adults with NNBPP. Surgeons use the same type of transfers in both populations. They must realize that although the nerve surgical repair technique is the same, the outcome regarding volitional control is not necessarily the same. The brain in the very young patient can process the changes induced by the peripheral nerve transfer better than in adults.

Author contribution Conception and design: MS, GdM, and MM. Acquisition of data: DB, MS, AL, GdM, and GB. Analysis and interpretation of data: all authors. Drafting the article: MS, MM, and RR. Critically revising the article: MM and MS.

Declarations

Conflict of interest The authors report no conflicts of interest concerning the materials or methods used in this study or the findings reported in this paper. No funding, grants, and financial or non-financial interests were involved directly or indirectly related to the work submitted for publication. All ethical standards than could be related during design, data collection, statistical analysis, writing, and editing this paper were accomplished, as well as any treatment of personal data from the patients involved.

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