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Restoration of sensory function and lack of long-term chronic pain syndromes after brachial plexus injury in human neonates

P. Anand[1] and R. Birch[2]

[1]*Peripheral Neuropathy Unit, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road, London and* [2]*Peripheral Nerve Injury Unit, Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK*

Correspondence to: Professor P. Anand, MD, Peripheral Neuropathy Unit, Imperial College School of Medicine, Area A, Ground Floor, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK
E-mail: p.anand@ic.ac.uk

Summary

Obstetric complications are a common cause of brachial plexus injuries in neonates. Failure to restore sensation leads to trophic injuries and poor limb function. It is not known whether the infant suffers chronic neuropathic or spinal cord root avulsion pain; in adults, chronic pain is usual after spinal root avulsion injuries, and this is often intractable. The plexus is repaired surgically in severe neonatal injures; if no spontaneous recovery has occurred by 3 months, and if neurophysiological investigations point to poor prognosis, then nerve trunk injures are grafted, while spinal cord root avulsion injuries are treated by transferring an intact neighbouring nerve (e.g. intercostal) to the distal stump of the damaged nerve, in an attempt to restore sensorimotor function. Using a range of non-invasive quantitative measures validated in adults, including mechanical, thermal and vibration perception thresholds, we have assessed for the first time sensory and cholinergic sympathetic function in 24 patients aged between 3 and 23 years, who had suffered severe brachial plexus injury at birth. While recovery of function after spinal root avulsion was related demonstrably to surgery, there were remarkable differences from adults, including excellent restoration of sensory function (to normal limits in all dermatomes for at least one modality in 16 out of 20 operated cases), and evidence of exquisite CNS plasticity, i.e. perfect localization of restored sensation in avulsed spinal root dermatomes, now presumably routed via nerves that had been transferred from a distant spinal region. Sensory recovery exceeded motor or cholinergic sympathetic recovery. There was no evidence of chronic pain behaviour or neuropathic syndromes, although pain was reported normally to external stimuli in unaffected regions. We propose that differences in neonates are related to later maturation of injured fibres, and that CNS plasticity may account for their lack of long-term chronic pain after spinal root avulsion injury.

Keywords: nerve; injury; obstetric; sensation; pain; plasticity

Abbreviation: SNS = sensory neurone-specific (sodium ion channel)

Introduction

Obstetric complications are the most common cause of brachial plexus injuries in babies, with an increasing incidence, ranging from 0.1 to 4% of live births in figures published from different countries (see Birch *et al*., 1998). There are two major risk factors—breech delivery and the heavy baby born by cephalic presentation (Giddins *et al*., 1994). A clinical study of the natural history of the motor deficits classified the patients into four groups (Narakas, 1987). In Group 1, the fifth and sixth cervical spinal nerves are damaged, and ~90% of these babies proceed to full recovery, which begins at no later than 2 months. In Group 2, the fifth, sixth and seventh cervical nerves are injured, with 65% of babies showing full spontaneous recovery. In Group 3, paralysis is virtually complete, although there is some flexion of fingers at or shortly after birth. Spontaneous recovery occurs in <50% of these children, and most of them are left with substantial impairment of function of the shoulder, elbow and forearm. In Group 4, the whole plexus is involved. Limb paralysis is complete, and there is a Horner's syndrome. Very few children make a substantial recovery. The disparity in limb length may be up to 20%. In Groups 3 and 4, the brachial plexus lesions are usually a combination of

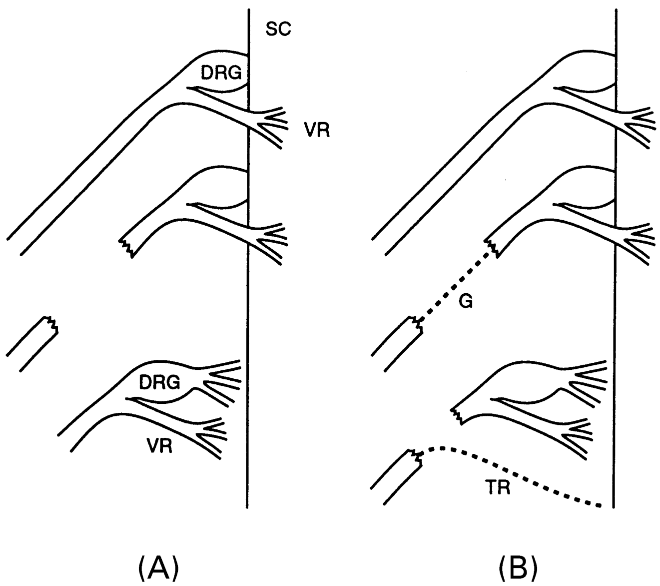

Fig. 1 Schematic representation of brachial plexus injuries (**A**) and their surgical repair (**B**). DRG = dorsal root ganglion; VR = ventral root; SC = spinal cord; G = graft; TR = transfer. (**A**) The upper roots are intact, the middle roots have a 'post-ganglionic' injury or rupture, distal to the DRG, and the lower roots are avulsed, a 'pre-ganglionic' injury. (**B**) The ruptured middle roots have been repaired by a nerve graft, and the lower avulsed roots by nerve transfer.

injuries, proximal (termed 'avulsion' or 'pre-ganglionic') and distal (termed 'rupture' or 'post-ganglionic') to the dorsal root ganglion. These terms would correspond to central and peripheral axotomy, respectively.

There have been no systematic clinical or quantitative studies of sensory and sympathetic function in obstetric brachial plexus palsy. Failure to restore sensation leads to injuries, trophic mutilation and poor use of the hand, even if there is some motor function. It is not known whether the child suffers chronic neuropathic or spinal cord root avulsion pain. Chronic pain is usual after brachial plexus injuries in adults, particularly following spinal root avulsion, when it can be extreme and intractable for years (Parry, 1984; Berman *et al*., 1996, 1998). Our previous clinical and animal experimental observations suggested that nerve injury in human and rat neonates does not lead to chronic pain behaviour or classical neuropathic syndromes commonly seen in the adult (Anand, 1992; Birch *et al*., 1998). Further, a significant proportion of adults develop referred sensations, and marked cutaneous hypersensitivity some years following plexus injury; the latter appears to be mediated by regenerating nerve fibres via abnormal central processing (Berman *et al*., 1998). It is not known whether these phenomena occur following neonatal brachial plexus injury.

It has been the practice in recent years to explore and repair the injured plexus in severe neonatal injuries, if no spontaneous recovery has occurred by 3 months, in an attempt to restore sensory and motor function. Diagnosis of these lesions is made by preoperative neurophysiological investigations (Smith, 1998) and by intraoperative inspection and neurophysiological studies. The rationale for the different strategies of repair has been described (Birch *et al*., 1998). Nerve grafts, using such nerves of cutaneous sensation as medial cutaneous of forearm, superficial radial nerve, lateral cutaneous nerve of forearm and sural nerve, are the usual methods of repair for nerve injury distal to the dorsal root ganglion (see Fig. 1). A number of techniques are used to repair spinal cord root avulsion injuries. In cases of multiple avulsions, of C7, C8 and T1, the proximal stumps of post-ganglionic ruptures of C5 and C6 are used to re-innervate the lower trunk (C8, T1). Selective transfer of the spinal accessory nerve to the ventral root and of the supraclavicular nerve to the dorsal component of the spinal nerve is suitable for one avulsed root. Extraplexual transfer, such as transfer of the spinal accessory to the suprascapular nerve and of intercostals to the lateral or medial cord, is also used. In avulsion, the dorsal root ganglia and dorsal rootlets are resected so that axons regenerating from adjacent post-ganglionic ruptures of spinal nerves forming the brachial plexus, or from such donor nerves as the supraclavicular or intercostals, may enter the distal stump. A pre-ganglionic lesion of afferent fibres is thus converted to a post-ganglionic lesion.

Using a range of non-invasive quantitative measures validated in adults (Anand *et al*., 1996; Facer *et al*., 1998), we have assessed sensory and sympathetic function in 24 patients aged between 3 and 23 years, who had suffered severe brachial plexus injury at birth (Groups 3 and 4) (Narakas, 1987). All but four patients had surgical repair of the injured plexus in infancy. It would not have been ethical to have a non-operated control group for this study, as surgical repair is of proven benefit in severe cases of obstetric brachial plexus injury; the four non-operated cases in this study were referred to our Unit some years after birth, when surgical repair of the injured plexus would not be practical. This study, the first of its kind, indicates the feasibility and necessity of examining sensory and nociceptive mechanisms in children with obstetric brachial plexus injury, and comparison with the findings with brachial plexus injury to older children and adults. Demonstration of good sensory recovery in the hand is also important for the further management of the patient, as it indicates a favourable functional outcome for remedial surgical procedures such as tendon transfers.

Methods

Patients

Patients with severe unilateral brachial plexus injury at birth (n = 24), and without clinical evidence of primary injury to the CNS, were recruited at the Royal National Orthopaedic Hospital. Ethical permission for the study was obtained from

Table 1 *Test results for all patients*

Patient no. (age, years)	Delay	Root level					Normal power (Raimondi)	Normal sweating	Normal hand sensation (modality)
		C5	C6	C7	C8	T1			
Non-operated									
1 (23)	–	R	A	A	A	A	No (0)	No	No
2 (17)	–	R	A	R	R	A	No (2)	No	No
3 (7)	–	R	R	A	A	A	No (1)	No	No
4 (7)	–	R	R	R	R*	R*	No (3)	No	No
5 (5)	3	R	R	R	A	A	No (3)	No	(Ulnar graft)
6 (4)	6	R	R	A	A	A	No (4)	Yes	Yes (all)
7 (4)	8	R	A	A	A	A	No (2)	No	Yes (all)
8 (6)	3	R	A	R	A	A	No (3)	No	Yes (all)
9 (5)	35	R	R	A	R	R	No (3)	No	Yes (ws, cs, pp)
10 (4)	5	R	R	R	R	A	No (3)	No	Yes (pp)
11 (6)	16	R	R	R	L	A	No (4)	Yes	Yes (vib, ws, cs)
12 (3)	2	R	R	R	R	L	No (3)	Yes	Yes (pp)
13 (5)	4	R	R	A	A	L	No (2)	Yes	Yes (ws, cs, pp)
14 (5)	8	R	R	A	A	L	No (3)	Yes	Yes (ws, cs, pp, jps)
15 (3)	3	R	R	L	A	I	No (4)	Yes	Yes (ws, cs, mf, pp)
16 (7)	13	A	R	R	A	L	No (2)	Yes	Yes (pp, cw)
17 (6)	5	L	L	R	R	A	No (3)	No	Yes (jps, mf, cw, cs, ws)
18 (7)	4	R	A	L	A	I	No (3)	Yes	No
19 (9)	5	R	R	R	A	A	No (2)	Yes	Yes (jps, mf, cw, cs, ws)
20 (6)	13	R	R	A	A	L	No (2)	No	Yes (ws, cs)
21 (7)	8	R	R	A	L	A	No (4)	Yes	No
22 (6)	18	R	R	R	A	A	No (1)	No	Yes (vib)
23 (7)	41	R	A	A	A	A	No (1)	No	No (late repair)
24 (4)	3	R	R	A	A	L	No (3)	No	Yes (vib, cw, ws, jps, pp)

Types of brachial plexus injury in non-operated (nos 1–4) and operated patients (nos 5–24), and the functional outcomes in the hand. Sensory recovery refers to all hand dermatomes for each modality. Motor function is on the Raimondi scale shown in parentheses. Delay indicates the number of months that the operation was delayed postnatally. A = avulsion (proximal to dorsal root ganglion), R = rupture (distal to dorsal root ganglion). L = lesion in continuity, I = intact. Sensory modalities: mf = monofilaments; cw = cotton wool; pp = pinprick; ws = warm sensation; cs = cool sensation; jps = joint position sense; vib = vibration sense. *Dorsal avulsion.

the local research ethics committee at the Royal National Orthopaedic Hospital and East London and City Health Authority Ethics Committee at the Royal London Hospital, and informed consent was given by parents/patients. The patient number, age at testing, diagnosis and test regions are shown in Table 1. The types of injury and their surgical repair are illustrated in Fig. 1.

Sensory testing

The tests were performed with the patient's eyes covered or closed, and accuracy of localization was recorded for each test. Pinprick, cotton wool and joint position sense were recorded as being present or absent. Both affected and contralateral, clinically unaffected, sites were studied with quantitative non-invasive sensory and sweat tests, which have been described fully previously (Anand *et al.*, 1996; Facer *et al.*, 1998) and are descibed, in brief, below. The patients were remarkably reliable witnesses, and performed the tests very consistently (see descriptions of patients below); the threshold values were similar to those obtained previously in normal young adult subjects. There were small differences of mean thresholds between different dermatomes for individual tests, but these differences were not statistically significant, and the lowest threshold value was therefore used for analysis. The quantitative tests were deemed 'abnormal' if the perception threshold was >2 SD above the mean for the same site in the contralateral limb ($n = 22$). As there may be age-related differences in thresholds, test values for patients 1 and 2 were compared with those previously obtained from subjects between 20 and 30 years ($n = 25$). The stimuli were applied at the following sites with focus on the hand, although there can, of course, be variation and overlap between dermatomes: C5, mid-lateral upper arm; C6, thumb; C7, middle finger; C8, little finger; T1, medial forearm.

Thermal thresholds

A Thermal Threshold Testing System (Somedic, Stockholm, Sweden) with a rate of rise in temperature of 1°C/s was used. A small thermode (15 × 25 mm) was placed at the appropriate site (palmar surface in the hand). The baseline temperature was set at a neutral point, between 30 and 32°C. Thermal thresholds were determined for cool and warm

Table 2 *Raimondi scale (hand function)*

Grade	Description
0	Complete paralysis or slight finger flexion of no use; useless thumb—no pinch; some or no sensation
1	Limited active flexion of fingers; no extension of wrist or fingers; possibility of thumb lateral pinch
2	Active extension of wrist, with passive flexion of fingers (tenodesis); passive lateral pinch of thumb
3	Active complete flexion of wrist and fingers; mobile thumb with partial abduction—opposition. Intrinsic balance; no active supination; good possibilities for palliative surgery
4	Active complete flexion of wrist and fingers; active wrist extension; weak or absent finger extension. Good thumb opposition, with active ulnaris intrinsics; partial pronosupination.
5	Hand Grade 4, with finger extension and almost complete pronosupination

sensation. Four separate consecutive tests were carried out for each modality. The mean difference from the baseline temperature was recorded as the threshold. For some subjects (who were <5 years old), the patient was asked to indicate verbally as soon as the stimulus was perceived, i.e. when the thermode temperature was felt as 'warm' or 'cool'; older subjects were able to press a button themselves to indicate this, as is the case with adults. The thermal thresholds in the contralateral intact limb did not differ significantly with the use of verbal or manual indication of change. 'Abnormal' (>2 SD above the mean) values for the children were: warm sensation >3.8°C, cool sensation >2.3°C (for adults aged 20–30 years, abnormal values were: warm sensation >3.9°C, cool sensation >2.6°C).

Monofilament threshold

Light touch thresholds were determined using Semmes–Weinstein hairs (made by A. Ainsworth, University College London, UK) placed on the skin, on bending the hair. The number of the hair detected reliably (three or more out of five trials) with the lowest force was recorded (in the hand, the lower of palmar or dorsum of finger values were recorded). Values were then transferred into the respective gram value. 'Abnormal' value: >No. 3 monofilament (0.0479 g), same as for adults.

Vibration perception threshold

These were measured with a biothesiometer (Biomedical Instrument Co., Newbury, OH, USA) placed at the distal interphalangeal joint of the appropriate finger, or a bony prominence in more proximal joints. Three ascending and three descending trials were carried out, and the values were averaged. 'Abnormal' value: >8 V; for adults >10 V.

Sweating studies

Sweating was measured in the palm with an evaporimeter (Servomed, Stockholm, Sweden) in $g/m^2/h$. The evaporimeter has two sensors which measure the relative humidity in an open cylinder at different distances from the skin surface; signals derived from these transducers are computed to provide first the partial pressure of water vapour gradient, and then the evaporation rate. 'Abnormal' value: <50% of contralateral palm.

Motor function

All the children were seen and motor function examined on at least two occasions before operation, and at regular intervals of 6 or 12 months afterwards. The systems for recording function were applied from about the age of 12 months. Return of motor function in the hand was measured by the system of Raimondi (Table 2) (Birch *et al*., 1998), and by recording the MRC grade for individual muscles.

Growth of the limb

Circumference was measured at the midpoint of arm and forearm. Tracings were made of the outline of the hand. The length and breadth of the digits were measured as a percentage of the normal hand. The length of three segments of the upper limb was measured: from the lateral tip of the acromion to the olecranon; from the olecranon to the tip of the ulnar styloid; and from the tip of the ulnar styloid to the tip of the middle finger.

Results

The sensory and sweating test results are summarized in Table 1. There was excellent restoration of sensory function, to normal limits in all dermatomes for at least one modality in 16/20 operated cases, and perfect localization of any restored sensation in all cases of sensory recovery. Thermal thresholds in the intact (contralateral) limb were similar to those reported in normal children (Hilz *et al*., 1998). The salient features are illustrated by the description of four patients below, and in Fig. 1. Recovery of function after spinal root avulsion was related demonstrably to surgery. In many cases, re-innervation of skin occurred through nerves transferred from a distant spinal region. No patient (or parent) reported any symptoms suggestive of neuropathic pain, although pain was reported normally in unaffected regions from between the ages of 2 and 3 years in all cases, and indeed on pinprick versus cotton wool testing in the clinic. Sensory recovery exceeded motor or cholinergic sympathetic recovery. Motor recovery was generally mediocre and certainly far less impressive than sensory recovery, particularly with delayed repair. As a general observation, recovery for shoulder and elbow function in our 20 operated cases was not better than that seen following repair of equivalent lesions in adults; in fact, it was probably rather worse. In no infant did we see normal power at the shoulder or elbow. On the Raimondi scale (see Table 1 for results, in parentheses), only three children reached grade 4, none reached grade 5. Seven children had a useless hand. All of the four non-operated and 10 out of the 20 operated cases had decreased sweating in the palm (i.e. <50% of the sweat rate in the unaffected palm). In three children, recovery of nociception occurred late, after 4 years or more, and this also appeared to be the case for motor recovery in some children.

Case 1 N.O.K. (Fig. 2A) non-operated

Clinical diagnosis: rupture C5; avulsion C6, C7, C8 and T1. Assessed at age 23 years, when first referred to this Unit.

History

She recovered sensation at the shoulder as a toddler, but not in the arm or hand of the affected limb. She has burnt herself on three occasions in the distal limb accidentally, without any pain. She denied spontaneous pain at any time, other than, interestingly, sharp pains in a right axilla scar, since an exploratory operation (not at our Unit) at the age of 4 years, when no repair was performed.

Examination

At C5 dermatome, there was normal sensation to monofilaments, pinprick, vibration, joint position sense and cooling, but a markedly elevated warm perception threshold (increase of 9°C, contralateral 2.8°C). At C6 to T1 dermatomes, sensation to all stimuli was absent. Mild Horner's syndrome was present and sweating was 30% of that of the contralateral limb. In terms of motor function, deltoid, infra- and supraspinatus were MRC Grade 4 and the clavicular head of pectoralis major was MRC 3. Elbow flexors were MRC 4. In length, the affected limb was shorter by 15%, the forearm by 25% and the digits by 40%, compared with the contralateral limb.

Conclusion

There appears to have been belated recovery across a rupture of C5, but complete lack of recovery for the rest of the plexus, consistent with avulsion of C6, C7, C8 and T1. She illustrates lack of spontaneous sensory recovery even years after multiple avulsion injury. It is notable that whereas this major plexus injury at birth was not associated with any pain, it was reported in the region of a scar following an operation at the age of 4 years, as is the case after similar surgery in some adults.

Case 5 S.F. (Fig. 2B) operated

Rupture C5, C6 and C7; avulsion C8 and T1. Operated on aged 3 months. Repair (by ulnar nerve graft) of all five roots, i.e. all post-ganglionic rupture immediately after surgery; therefore, recovery was by regeneration after repair. In this case, the ipsilateral ulnar nerve was used as a graft, with the superficial radial nerve and medial cutaneous nerve of the forearm, because of the extent of the lesion and the considerable gap between the prepared nerve stumps. Five strands of ulnar nerve and three strands of cutaneous nerves were used as grafts. Assessed age 5 years.

History

He initially did not feel his arm, and there was Horner's sign. He did not give the appearance of pain, and had no sleep disturbance. Aged 1 year, he responded to stimuli at his shoulder, and in later years throughout the arm with the exception of the little finger and ulnar border of the hand (according to his parents). He reported pain elsewhere in the body accurately by the age of 2, but has never complained of pain in the injured arm.

Examination

Cotton wool and pinprick sensation was normal in the affected limb, but absent in the ulnar distribution in the hand, and normal in the upper arm. Vibration sensation was 12 V in the index finger on the affected side, >50 V (upper limit of biothesiometer) in the little finger and 6 V in the contralateral index finger. Joint position sense was normal in all but the little finger, where it was absent. Warm sensation was 2°C in the median territory of the affected arm and 1.8°C in both territories in the unaffected arm, and cool thresholds were 1.3°C in the right median territory and 0.9°C in the unaffected arm; thresholds at the ulnar territory were beyond test 'safety' limits (>42°C, <10°C). With monofilaments, he was able to feel No. 5 (0.132 g) in the right median nerve territory, and was unable to feel No. 20 (263 g) in the ulnar nerve territory. Localization of sensations was instantaneous and perfect.

Sweating was 55% of the opposite palm in the median nerve territory (thenar eminence) and 25% in ulnar nerve territory (hypothenar eminence).

There was good recovery into muscle at the shoulder with active elevation against resistance (M4) to 170°, active lateral rotation of 30°, with medial rotation of 80°. Power of triceps was MRC Grade 4, and of elbow flexors was Grade 3. The Raimondi grade for the hand was 3, and power of the FDP (flexor digitorum profundus) and FPL (flexor pollicis longus) was MRC Grade 4, and that of APB (abductor pollicis brevis) and opponens was MRC Grade 4. Wrist extension was MRC Grade 3 and digital extension MRC Grade 2. There was no recovery of FCU (flexi carpi ulnaris) or the ulnar innervated intrinsic muscles.

The arm was 3 cm shorter (12%), the forearm 2.5 cm shorter (12%), the thumb and index finger were 20% shorter and the little finger 50% shorter than in the undamaged upper limb.

Conclusion

All recovery in this case came through the repair. There was neither motor nor sensory recovery for the ulnar nerve (little finger). The latter demonstrates the patient's reliability as a sensory witness, and lack of significant spontaneous collateral sprouting in the periphery. The relationship of innervation to limb length is clearly demonstrated.

Case 6 M.D. (Fig. 2C) operated

Rupture C5 and C6; avulsion C7, C8 and T1. Repair aged 4 months. Seven cutaneous grafts were used, using the ipsilateral medial cutaneous nerve of forearm and superficial radial nerve. Proximal to injury, C5 was grafted to distal C5, C6 and C7; C8 and T1 were sutured directly to C6. Assessed when aged 4 years.

History

There was gradual improvement of sensory and motor function from the age of 14 months. The patient and parent denied pain in the affected arm.

Examination

She was able to sense cotton wool, pinprick and joint position equally well in both hands, and localize accurately. Warm sensation threshold was <2.1°C across the normal hand, and <2.2°C across the affected hand. Cool sensation was equal at <1.5°C across either hand. Her sweat rate was identical in both palms. Monofilaments: No. 12 at C5, No. 10 at C6, No. 5 at C7, No. 4 at C8 and No. 3 at T1.

In terms of motor function, there was useful recovery into the shoulder, with elevation against gravity to 50°, 30° of active lateral rotation, and 70° of medial rotation against resistance. Elbow flexion and wrist extension were MRC Grade 3. The long flexors and intrinsic muscles of the hand were graded at MRC Grade 4. After transfer of a wrist flexor, the hand was graded at Raimondi 4. Sweating was 60% of that in the intact palm.

The arm was shorter by 15%, the forearm by 18% and the digits by 25% compared with the right upper limb.

Conclusion

In this case, two stumps, C5 and C6, were used to re-innervate the whole limb. The grafts from proximal C5 to distal C5, C6 and C7 restored some function at the shoulder, elbow and wrist and re-innervated the skin of the thumb, index and middle fingers. The suture of proximal C6 to distal C8 and T1 regained useful power in long flexors and intrinsic muscles and re-innervated the skin of the ring and little fingers. Sensation was rather better for these two digits (see monofilaments), with the sensory pathway presumably via the C6 spinal cord segment; the correct localization thus provides evidence for CNS plasticity.

Case 7 R.H. (Fig. 2D) operated

Rupture C5, with avulsion C6, C7, C8 and T1. Repair performed at age 6 months. The fifth cervical nerve was sutured to C8 and to T1; intercostal nerves T3, T4 and T5 were transferred to the lateral cord (distal C5, C6 and C7); accessory to suprascapular nerve transfer was also performed. In this particularly severe case, only one nerve (C5) showed a reparable lesion; all others were avulsed. C5 was transferred to C8 and T1 with the aim of restoring some hand function. The lateral cord was re-innervated by intercostal nerves 3, 4 and 5 with the aim of regaining elbow flexion and innervating the skin of the thumb, the index and the middle fingers. Assessed when aged 4 years.

History

Some motor and sensory recovery was observed from the age of 1 year. He denied any pain in the arm.

Examination

He was able to localize cotton wool and pinprick sensation in both hands and was able to feel a pin in the affected side. His monofilament and vibration thresholds were identical in both hands, as was joint position sense. His warm sensation was 3.1°C at C5, 3.8°C at C6, 4.1°C at C7, 3.6°C at C8 and 3.3°C in T1 on the affected side. His cool sensation was 2.0°C at C5, 3.9°C at C6, 3.8°C at C7, 2.3°C at C8 and normal in T1. The respective values were <3.4°C for the unaffected hand for warm sensation, and <2.2°C for cool sensation. There was no useful motor recovery at the shoulder and elbow. The hand was graded as Raimondi 2, with a pinch grip between thumb and index. FCU was MRC Grade 4, FDP and FPL were Grade 3, and intrinsic muscles of the hands were Grade 2. The intercostal transfer failed to restore elbow flexion, although electromyography 24 months after the operation showed some volitional motor unit activity. Sweating was 70% of that of the intact palm. There was considerable atrophy of the limb. The arm and forearm were 20% shorter than on the left side, and the digits diminished by 25%.

Conclusion

Motor recovery for shoulder and elbow has been poor, and there has been only limited recovery of motor function within the hand. In contrast, the accuracy of localization and the

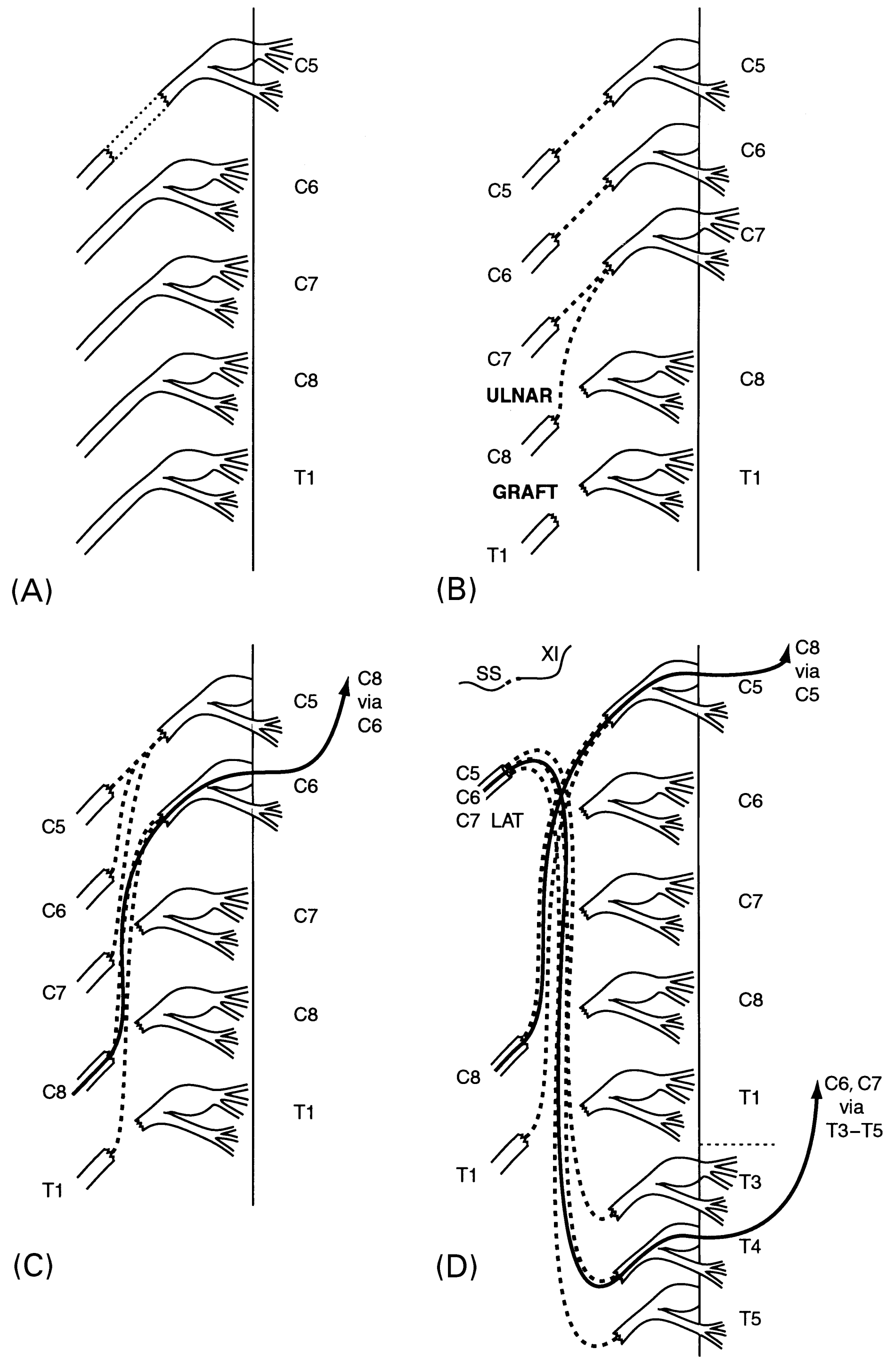

Fig. 2 Schematic representation of brachial plexus injuries in Case 1 (**A**), Case 5 (**B**), Case 6 (**C**) and Case 7 (**D**). See Table 1 and Results for the description of the cases. Case 1 (N.O.K., **A**) was non-operated, with a clinical diagnosis: rupture C5; avulsion C6, C7, C8 and T1. Case 5 (S.F., **B**) had rupture C5, C6 and C7; avulsion C8 and T1, and repair was by ulnar nerve graft. Case 6 (M.D., **C**) had rupture of C5 and C6; avulsion C7, C8 and T1. The sensory pathway for the little finger was presumably via the C6 spinal cord segment. Case 7 (R.H., **D**) had ruptured C5, and avulsed C6, C7, C8 and T1. Afferent impulses from the thumb and index finger probably entered the spinal cord through the three intercostal nerves T3, T4 and T5, and from the little finger through C5.

quality of cutaneous sensation are particularly good. Afferent impulses from the thumb, index and probably the middle finger enter the spinal cord through the three intercostal nerves T3, T4 and T5; afferent impulses from the little and probably ring fingers enter the spinal cord through the fifth cervical nerve. This case provides strong evidence for CNS plasticity. Similar results were seen in four other cases where the lateral cord was re-innervated by intercostal nerves.

Discussion

Using non-invasive quantitative measures validated in adults, we have assessed for the first time sensory and sympathetic function in patients who suffered severe brachial plexus injury at birth. The recovery of function after spinal root avulsion was related demonstrably to surgery, as non-operated cases provided no evidence of spontaneous recovery when an avulsion was diagnosed on clinical grounds, even years after surgery (see Case 1, Fig. 2A). Further, there was no evidence of significant collateral sprouting in the periphery, e.g. there was persistent and profound loss of sensation in the ulnar nerve territory when this nerve had been removed from the distal affected limb, to be used in a proximal plexus repair (see Case 5, Fig. 2B). Apart from demonstrating the restoration of protective sensation, our findings have implications for the value of further surgical measures, such as tendon transfers, to improve hand function in such patients (Birch *et al*., 1998).

There were remarkable differences in these patients in comparison with adults who have suffered similar injuries. There was excellent restoration of sensory function in the majority of cases. Moreover, there was evidence of exquisite CNS plasticity, i.e. perfect localization of restored sensation in avulsed spinal root dermatomes, now presumably routed via nerves that had been transferred from a distant spinal region (see Cases 6 and 7, Fig. 2C and D). There was no evidence of chronic pain behaviour or neuropathic syndromes, although pain was reported normally in unaffected regions. In contrast, any sensory recovery is usually disappointing in adults with such lesions, with or without surgical repairs; the stimulus modality is often misidentified, the sensation poorly localized and usually referred to other sites, and there may be allodynia or hyperalgesia associated with re-innervation (Berman *et al*., 1998). Severe chronic pain is also usual after spinal root avulsion in adults, when it can be intractable for years or even decades (Parry, 1984; Berman *et al*., 1996, 1998).

There are other important differences between the adult lesions and obstetric brachial plexus palsy. One feature of recovery through grafts in obstetric brachial plexus palsy is its slowness, considering the distance through which new axons must grow. The rate of recovery may be slower than in adults: in some cases, motor recovery of hand function was not seen until nearly 4 years had passed, and sensory recovery, particularly of nociception, until the age of 5 years. Furthermore, motor recovery, though often good, is never complete. The latter may reflect loss of ventral horn cells following root avulsion, which may be more severe in the young than in the mature animal, and may explain the discrepancy between the degree of motor and sensory recovery. There did not appear to be any correlation of surgical delay with functional outcome on the basis of the present data. As neonates are operated on relatively late (2 months or more after injury), unlike most adults, this issue may be resolved only when neonates are operated on with shorter delays.

It may be hypothesized that lack of long-term chronic pain syndromes seen after peripheral nerve injuries in neonates, and slowness of sensory recovery, could be attributed to delayed maturation of peripheral nerves, particularly at nodes of Ranvier. While this proposed mechanism may partly explain lack of pain phenomena when the injury is distal to the dorsal ganglion, the lack of spinal root avulsion pain is likely to be the result of CNS plasticity, as discussed below. It should be emphasized that our present study does not address the issue of pain phenomena in subjects with obstetric brachial palsy before they are ~3 years old. However, whereas the subjects all responded to painful stimuli and reported them appropriately during development in unaffected regions, both patients and parents denied any evidence of pain in the affected limb. It is interesting that the children with obstetric brachial plexus injury with shoulder abnormalities reported pain in the shoulder when they were treated by physiotherapy. Young children do, of course, develop and report chronic pain associated with other pathologies, such as arthritis and cancer (Anand and Carr, 1989). The lack of chronic pain behaviour or neuropathic syndromes was in accord with our previous observations (Anand, 1992; Birch *et al*., 1998). Limb amputations in young children (less than ~3 years old) and more peripheral limb nerve injuries also appear not to lead to chronic pain syndromes seen in some adults (Anand, 1992); this observation led to a study of pain-related behaviour in rats, using the model of sciatic nerve axotomy leading to autotomy (self-mutilation) (Wall *et al*., 1979). Rats lesioned earlier than 3 weeks after birth failed to show autotomy, whereas those lesioned thereafter showed levels of autotomy seen in lesioned adult rats (Anand, 1992). These observations are supported by a review of the literature where, although phantoms are described in some young children after limb amputation and aplasia, there is no reference to chronic neuropathic pain in the majority of studies (Poeck *et al*., 1964; Weinstein *et al*., 1964), but intermittent phantom pain phenomena have been reported in one study (Melzack *et al*., 1997). It is notable that nerve conduction velocities achieve adult values at ~3 years and ~3 weeks of age in humans and rats, respectively, the potential significance of which is discussed below.

The ion channels in human axons are fundamentally similar to those of other species (Scholz *et al*., 1993). Sodium channels in peripheral nerves in the rat show marked increases and clustering during postnatal development of the nervous system, up to the age of 3 weeks (Vabnick *et al*., 1996, 1998; Safronov *et al*., 1999); their development to an adult distribution in rat nerves coincides with both adult nerve conduction velocities and autotomy after peripheral nerve injury (i.e. at ~3 weeks postnatally). Similarly, conduction velocity studies in normal human subjects show that sensory and motor conduction in the median nerve is <50% of normal values at birth, rising to normal values at ~2 years of age (Brett, 1991); the course of maturation of unmyelinated afferents is not known. Chronic neuropathic pain syndromes are not apparent in humans before nerve conduction velocities approach adult values (i.e. before 3 years postnatally). Clinical and basic experimental studies have shown that sensory neurones become hyperexcitable after axonal injury, and electrophysiological studies have suggested that this may be at least partly the result of changes in sodium ion channel expression and clustering. Sodium channels, including sensory neurone-specific 1 (SNS1) and SNS2, accumulate at the tips of injured axons and in adult human painful neuromas (Coward *et al*., 2000; Yiangou *et al*., 2000). As some nerve tissues must be removed as part of the surgical repair procedure, we have attempted to investigate in these tissues differences between neonate and adult injured nerves (Anand *et al*., 1997). Our findings reveal differences which may be significant; for example, neonate neuromas lacked the NaN/SNS2 180 kDa molecular form, which was strongly present in adults (Yiangou *et al*., 2000). Structural and functional plasticity also occurs in the CNS following peripheral nerve injury during development (see Alvares and Fitzgerald, 1999), and particularly after spinal cord root avulsion injury, as discussed below. However, extrapolation across species at different stages of development deserves caution, in the absence of CNS tissue data from humans with brachial plexus injury.

The long-term central pain of avulsion injury, which is such a major problem in adults, has not been encountered in any child with obstetric brachial plexus palsy. The perfect localization of the perceived sensory stimulus, and lack of referred sensation or chronic avulsion pain syndromes may all be the result of CNS plasticity. This is reflected in the change of limb dominance. In almost every case of significant lesion, the injured side becomes non-dominant: only a few children change dominance after recovery, and never before the age of 4 or 5 years (Birch *et al*., 1998). In adults, deafferentation of the spinal cord is likely to be associated with plasticity at higher levels in the CNS (Ramachandran *et al*., 1992; Halligan *et al*., 1993), and the degree of cortical reorganization has been highly correlated with the severity of phantom pain following limb amputation (Flor *et al*., 1995). Subjects with congenital absence of a limb and no phantom phenomena did not show cortical reorganization (Montoya *et al*., 1998). Functional neuroimaging and physiological studies may reveal differences of central plasticity between adults and neonates with brachial plexus nerve injury. Such studies, and those of ion channel distribution, may indicate novel strategies to improve sensory function and relieve pain in adults with nerve injuries.

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