REHABILITATION IN THE DISORDERS OF PERIPHERAL NERVES

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Rehabilitation of brachial plexus injuries in adults and children

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Management of brachial plexus injury sequelae is a challenging issue in neurorehabilitation. In the last decades great strides have been made in the areas of early diagnosis and surgical techniques. Conversely, rehabilitation of brachial plexus injury is a relatively unexplored field. Some critical aspects regarding brachial plexus injury rehabilitation have to be acknowledged. First, brachial plexus injury may result in severe and chronic impairments in both adults and children, thus requiring an early and long-lasting treatment. Second, nerve damage causes a multifaceted clinical picture consisting of sensorimotor disturbances (pain, muscle atrophy, muscle weakness, secondary deformities) as well as reorganization of the Central Nervous System that may be associated with upper limb underuse, even in case of peripheral injured nerves repair. Finally, psychological problems and a lack of cooperation by the patient may limit rehabilitation effects and increase disability. In the present paper the literature concerning brachial plexus injury deficits and rehabilitation in both adults and children was reviewed and discussed. Although further research in this field is recommended, current evidence supports the potential role of rehabilitation in reducing both early and long-lasting disability. Furthermore, the complexity of the functional impairment necessitates an interdisciplinary approach incorporating various health professionals in order to optimizing outcomes.

KEY WORDS: Muscle atrophy - Pain - Neuronal plasticity - Upper extremity deformities, congenital.

Brachial plexus injury (BPI) is a relatively frequent condition leading to a complex functional impairment of the upper limb and disability. It is caused mainly by traumatic accidents resulting principally in traction forces, a wound or a compression of the plexus on the hard surface of the neighbouring structures (ribs, vertebral bodies or muscles). Sometimes it can be caused by tumors,[1] inflammatory diseases or by diagnostic or therapeutic procedures. If it occurs during birth it is defined obstetric brachial plexus palsy (OBPP).

The first descriptions of BPI in children were carried out by Smellie in 1764 and Duchenne in 1872 and both suggested traction of the arm as a possible cause. Subsequently, in 1874, Erb described a similar palsy in adults and suggested that traction or compression of the C5 and C6 roots could be the cause.[2] From an anatomical point of view, the brachial plexus originates from the anterior rami of cervical (C5-8) and thoracic (T1) segments of spinal cord. Multiple divisions of brachial plexus components create a network, giving rise to nerves for muscles and skin of chest and upper limb. It is not uncommon to find anatomical variations in formation, length and caliber of the different components of brachial plexus.[3, 4]

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Treatment of impairments due to lesions of this complex anatomical structure is a relatively unexplored field of neurorehabilitation, which involves a variety of issues about diagnosis, classification and, above all, rehabilitation.

As regards rehabilitation, it is a long-lasting treatment because improvements are very slow. Limited muscle activity may be observed even months after the damage and improvements after surgery may only be seen after 3 or 4 years of treatment. Time of recovery depends on many variables, such as the complexity of injury and timing of diagnosis and treatment. When dealing with children, the time for reinnervation is not shorter than in adults, and certainly not age related.[5] Therefore, it requires a lot of resources in terms of economic investments and time, by both the multidisciplinary team and the patients' caregiver.

Moreover, patient cooperation in the rehabilitation project is crucial to ensure the best outcome. In addition, adult patients usually have psychological issues, such as anxiety, depression, as well as difficulty in returning to work, thus having a decreased quality of life.[6, 7]

In the present paper the literature concerning BPI deficits and rehabilitation in both adults and children was reviewed and critically discussed.

Epidemiology of brachial plexus injuries

As regards to the epidemiology of BPI, it is important to make a distinction between adults and children.

Concerning epidemiology of adult brachial plexus damages, there are scarce and old data regarding the rate of occurrence in North America. At the end of 1990s Midha provided a prevalence of BPIs in the multitrauma population as approximately 1.2%.[8]

Although recent and exact data are lacking, BPI usually affects young healthy adults, and in particular male patients (89%). Age of patients ranges between 14 to 63 years, with a mean of 29 years and a median of 25 years of age. Fifty percent of patients are between 19 and 34 years old.[8, 9]

Between 44% and 70% of BPI are caused by traumatic injuries, mostly occurring in motorcycle accidents, during sporting activities, or at the work place.[8, 10-12]

In particular, motorcycle accidents account for 22% of injuries, since it is estimated that 4.2% of patients involved in motorcycle accidents have plexus damage.[8, 11, 12] In adults, another notable cause of BPI is iatrogenic lesion. In this group, traumas are often possible causes, for example during surgical and anesthetic procedures.[1] In these cases, the mechanism of trauma is due to stretching and compression secondary to inappropriate positioning of the upper limb during surgery, or to a direct lesion by interventions on the shoulder, the posterior triangle of the neck, and axilla.[10,13, 14] Even though traumatic mechanism accounts for a significant number of brachial plexus iatrogenic lesions, there are some non traumatic less frequent causes of damage, such as adjuvant radiation.[10, 15] The incidence of iatrogenic BPIs as a whole is difficult to estimate. Nonetheless they can be a significant cause of major disability.[16-20]

In regards to epidemiology of brachial plexus damage in children, OBPP is by far the most frequent etiological condition. Incidence of OBPP in the available literature ranges between 0.38 and 1.56 per 1000 live births. This wide variability may depend on the difference in the type of obstetric care and in the average birth weight of infants in different geographic regions.[21]

For instance, a recent study reported an incidence of OBPP in USA of about 1.51 cases per 1000 live births.[22] Similar results are reported by a Canadian study, where the incidence is estimated to be between 0.5 and 3 injuries per 1000 live Birth.[23] As to European countries, a Dutch study reported an incidence of 4.6 per 1000 births. A further interesting finding of this study is that a complete neurological recovery occurred in 72.6% of cases.[24]

OBPP represents a frequent cause of litigation against physicians or other professionals involved in health care. At present, 4.2% of all medical malpractice claims against obstetricians are related to trauma during birth.[25]

Some perinatal risk factors for OBPP are birth weight >4 kg, maternal diabetes mellitus, maternal obesity or excessive weight gain, prolonged pregnancy, prolonged second stage of labor, persistent fetal malposition, and breech delivery.[26] Other risk factors for OBPP include multiparous pregnancies, previous deliveries resulting in brachial plexus birth palsy, and difficult operative delivery.[21]

There is no consensus regarding caesarean sec-

tions and the risk of OBPP. Some studies report it to be a protective factor, while in other studies it accounts for 1% to 4% of cases of lesion.[22, 26]

Similar risk factors have been noticed in a Swedish study for shoulder dystocia, which is frequently associated to OBPP, probably due to the supplementary effort needed during delivery in these conditions. However, a high percentage of babies with OBPP (54%) without known risk factors before birth or during delivery was also reported.[22]

Classification

Classification of brachial plexus damages has been historically developed in relation to traumatic etiologies causing upper limb traction. Sequelae of traction injuries can be subdivided into rootlet avulsion or rupture.[3]

Two possible types of avulsion are peripheral and central avulsion. In peripheral avulsion, traction forces overcome the resistance of the supports that keep rootlets attached. On the other hand, in central avulsion, the movement of the spinal cord leads to spinal bending and therefore rootlet avulsion.[4]

Ruptures can be located both at a pre- or postganglionic level.

Since causes and mechanism of traumas are very different in adults and children, different types of classifications in these two groups have been put forward. Usually available literature classifies adult lesions on the basis of lesion site, distinguishing supraclavicular, retroclavicular or infraclavicular plexus lesions.[5] In children, on the contrary, classification is based on which roots are involved.

As to adults, supraclavicular injuries involve roots and/or trunks, and account for approximately 75% of brachial plexus lesions; true avulsions with subclavian artery rupture can be associated. Often these lesions are caused by a trauma that produces violent head and neck movement away from the ipsilateral shoulder. Retroclavicular lesions involve brachial plexus divisions and are the least common; vascular damage is often present.[10]

In infraclavicular injury distal branches are involved. Vascular lesions are associated in about 30% of cases. The mechanism of trauma is often a violent injury to the shoulder girdle, particularly abduction trauma and anterior shoulder dislocation.

As far as outcome is concerned, in supraclavicular lesions upper limb recovery is worse than in infraclavicular lesions. Moreover, supraclavicular injuries more frequently require surgical exploration (52% of cases *vs.* 17%).[8]

As regards children, historically, the first classification was based on the observations carried out by Erb and Klumpke. Erb described both C5 and C6 root avulsions and upper trunk lesions, whereas Klumpke observed the C8-T1 injury pattern, which is not common as an isolated form.[27]

Subsequently, Narakas *et al.* suggested a classification which partially overlapped with the previous findings. They identified four types of lesions.[28] In type I (upper Erb's), C5 and C6 roots are involved with spontaneous recovery in over 80% of cases. In these children weakness of shoulder abductors, external rotators and elbow flexors is generally observed. Type II lesion (extended Erb's) involves C5-C7 level and clinical presentation is similar to type I with the addition of drop wrist. These children show a good recovery in 60% of cases.

Type III injury is characterized by involvement of C5-T1 roots with a complete flaccid paralysis. Spontaneous recovery occurs in 30-50% of cases with a functional hand in many patients.

In type IV clinical findings are the same as in type III, but with the addition of Horner syndrome. The roots involved are C5-T1. These children show the worst spontaneous recovery.

In addition, Brunelli and Brunelli described lesions of the C7 root as "intermediate palsy", usually due to anterior to posterior traction.[29] An associated variable involvement of the upper or the lower plexus was found, depending on the mechanism of trauma. Indeed, trauma in abduction causes primarily lower plexus injury, whereas downward traction provokes predominantly upper plexus damage.

Al-Qattan *et al.* recently introduced a modification in Narakas'classification, subdividing type II into two categories: IIa and IIb.[30] Type IIa includes children with extended Erb's palsy and recovery of early (within two months) wrist extension, whereas in type IIb children do not show early wrist extension. Patients who belong to type IIa show a significantly higher percentage of good spontaneous upper limb recovery than those belonging to type IIb.[30]

Assessment

Clinical evaluation

Early diagnosis of BPI is of most importance, both in newborns and in adults, since secondary damage could lead to disability and functional impairment. Indeed, muscular atrophy and visco – elastic changes in muscles, ligaments, and joints can hamper normal use of limbs, even when reinnervation occurs.

Despite diagnosis is typically quite simple and clinical evaluation immediately leads to a correct identification of the injury, sometimes other medical conditions, such as sepsis with localization at the glenohumeral joint or infant cerebral palsy, can show a similar clinical pattern.[10]

In the acute phase, clinical history is useful in identification of the traumatic mechanism of injury in adult patients. In addition, diagnosis could be supported by acute pain onset on the upper limb, with a distribution that often reflects the line of application of force during trauma. Skin bruising and focal ecchymosis can also be observed.[10] A detailed neurological clinical examination can suggest a general identification of extent of lesion; the area of motor paralysis and sensory loss generally correlate with site and extension of BPI (see also somatosensory deficits for details).

Sympathetic damage is often associated with a C8-T1 lesion.[10]

It is also important to evaluate a possible appearance of a tingling sensation (with a precise neuroanatomical distribution) exacerbated by percussion of a nerve trunk in the posterior triangle of the neck (positive Tinel's sign). Generally it correlates with a post-ganglionic damage.[31]

In regards to children with OBPP, a detailed and thorough neurological examination, as in adults, is of most importance to support clinical diagnosis.

It is necessary to look for associated signs, such as torticollis, cutaneous colour and trophic changes, contralateral arm involvement and bone fractures (especially ipsilateral clavicle fractures).[23] Usually newborns with OBPP and associated torticollis tend to look away from the affected arm.

Somatosensory deficits, as well as facial nerve palsy, phrenic nerve damage (seen as thoracic and abdominal asymmetry), sympathetic involvement and Horner syndrome must be carefully detected.[32]

The site and extent of the lesion can be suggested by head and neck position, as well as shoulder and upper limb posture. For example, Erb's or Klumpke's palsy sometimes can be suspected by observing the placement and movement of the affected arm.[23]

As to shoulder girdle, it is necessary to rule out shoulder dislocation and winging of the scapula (correlated to long thoracic nerve injury). Furthermore, segmental range of motion and movements have to be observed. For the evaluation of single movements, with and without gravity, the Active Movement Scale [33] is frequently used in children with OBPP.[23]

Instrumental examination

Instrumental examination supports clinical evaluation in BPI detection, both in adults and children.

As to adults, in the past years, myelography with water – soluble agents was found to be more accurate than MRI in the detection of nerve rootlets inside the spinal canal. Currently, computed tomography - myelography (CT – myelography) is considered the gold standard to identify the site of lesion and the amount of damage.[34] Radiograms are used to detect fractures and/or dislocations of ribs (especially the first rib), elevation of ipsilateral hemidiafragm (in the latter case it could be a possible damage of C5), shoulder girdle depression, and dislocation of the scapula.

Neurophysiological studies are helpful, before and during surgery. Intraoperative sensory evoked potentials (SEPs), combined with paraspinal muscle electromyography (EMG), can be helpful in the identification of possible selective avulsion of ventral or dorsal rootlets and to distinguish between pre- and post-ganglionic lesions. Indeed, the amplitude of sensory nerve action potentials (SNAPs) is normal in pre-ganglionic injuries whereas is absent or reduced in postganglionic injuries.[35, 36] As regards EMG, it can provide information about muscle denervation from axonal damage and prognostic information regarding reinnervation. The ideal timing to perform EMG ranges between 3 and six weeks after injury. As to reinnervation, EMG is characterized by polyphasic motor units, with low amplitude configuration; new terminal sprouts can be identified within 1-2 months after damage.[37]

As to OBPP, magnetic resonance imaging (MRI) and ultrasound scan (US) are often used, basing on the low compliance of newborns and the need to use less invasive techniques.

Fast spin-echo sequence MRI is considered more suitable than CT myelography, because of its rapidity of execution and the reduced doses of sedation required. Fast spin-echo MRI can also identify associated pseudomeningoceles, indicating possible rootlets avulsions.[38]

In US technique, anatomical landmarks such as the anterior tubercles of transverse vertebral processes can lead to a proper identification of roots.[39] A root injury can be inferred by the demonstration of an increased nerve cross sectional area.[40]

In addition, differential diagnosis between pre- and post-ganglionic injury can be accomplished through US.[41]

Sequelae of brachial plexus injury

Muscle atrophy

Development of muscle atrophy is a remarkable result of denervation. Denervated muscles undergo several structural and neurophysiological alterations, which cause contractility deficits and changes in excitability, resulting in muscle atrophy. This topic has been widely discussed in literature based on studies on animal models.

In rats, after denervation, a progressive loss of weight and reduction of muscle fibre diameter occurs within two weeks.[42, 43] At a microscopic level, muscular fiber structure is subverted. In particular, sarcomeric disorganization, myofibrillar disruption, changes in the number of ribosomes and in the number and size of mitochondria, and changes in sarcoplasmic reticulum morphology are reported[44]. As a result, altered structural properties lead to a slowed contraction speed. Besides morphologic alterations, changes in excitability contribute to pathological contractile activity. After only 7 days from denervation, a reduction in the resting membrane potential by 10-15 mV was observed in rats, with smaller and slower action potentials than in controls.[45-49] Furthermore, a reduced velocity in the impulse conduction was recorded.[46, 48] Action potential changes were explained by a decreased Na+ current as a consequence of an increased Na+ channel inactivation during the impulse.[50, 51] Effectiveness of ultra-slow processes of Na+ conductance inactivation tended to decrease after 6 days of denervation, as a mechanism of membrane adaptation. That is, the partial removal of ultra-slow Na+ inactivation results in the capacity of voltage-dependent ion channels to operate in a condition of chronic depolarization.[52] Another adaptive change in a denervated muscle is the development of supersensitivity to acetylcholine (ACh). After 5-10 days acetylcholine receptors increase their extrajunctional density and distribution.[53] In about two weeks the increased sensibility to ACh in extrajunctional membrane reaches a peak, and then begins to decrease at about three to four weeks.[54]

It is interesting to note that the different types of muscle fibers are not homogeneously affected by atrophy. For instance, a faster rate of atrophy was found in the soleus (typically slow-twitch) with respect to the extensor digitorum longus (typically fast-twitch) muscle in rats,[55] while in dogs the gastrocnemius underwent a slower atrophy than the anterior tibial muscle.[56] Other studies reported a preferential atrophy of histochemical type 2 (fast) with respect to histochemical type 1 (slow) fibers in fast-twitch,[57-60] but not in slow-twitch muscles.[58, 61] In humans a difference was found between early and later effects of denervation.[60] Two to four days after denervation the most commonly reported change is an alteration of contractile properties, mainly due to an altered muscle activation process.[48, 62-64] In particular, a few days after denervation there is a reduction of developed tension in the stimulated muscle. This observation can be explained by alterations of the electrical properties of the muscle cell membrane, which preclude the generation of high frequency action potentials, and thus a complete activation of the muscle.[47, 63] Furthermore, fibrillation activity starts in the first few days, with spontaneous and uncoordinated contractile activity of the denervated muscle, occurring in coincidence with the fall in resting membrane potential.[65] Fibrillation activity reaches a peak in a few days, and then decreases, especially in slow type muscles.[66, 67] Afterwards, changes in the pattern of myofibrillar protein expression and muscle fiber composition are observed some weeks later.[60]

A temporal progression in the development of human muscle atrophy has been described.[60] Between 2 and 3 months a decrease of 50% in fibers diameter appears, while streaks remain intact. At 2 and 4 months, morphological activation of satellite cells is found, simultaneously with a decrease in fibril number, myofiber and capillary death, and deposition of massive amounts of interstitial collagen.

At the same time, condensation and fragmentation of nuclear chromatin appear in some nuclei, while later there is a loss in normal staining density of mitochondrial matrix. With increasing denervation time, mitochondria become smaller and more globular in shape, with sparsely arrayed cristae. All these changes contribute to reduce the restorative capacity of the denervated muscle.[60] Gross muscle and muscle fiber atrophy continues in the period between 2 and 7 months of denervation, with dense mats of collagen fibers surrounding remaining muscle fibers. Initial streak rarefaction begins around 1 year after denervation, while by 18 months a substantial reduction in cross sectional area and characteristic changes in the sarcoplasmic reticulum are observed. Sarcoplasmic reticulums become more irregular and lose their close relationship to the A-I junctions.[60] At two years muscular fiber fragmentation and disintegration is evident. Substitution with adipose and fibrous connective tissue occurs between 1 and 3 years postdenervation, leading to a loss and replacement of muscle fibers.[68]

Pain

Pain is a major complaint in adult patients with a brachial plexus avulsion or traction injury. Aside from nociceptive pain resulting from ligament and joint injuries at the time of initial trauma, the main concern is neuropathic pain derived from nerve injury. This kind of pain usually appears after preganglionic injuries of the brachial plexus and is more frequent in patients with total palsy.[69-72] It is reported that nearly 80% of patients with complete brachial plexus palsy after avulsion injuries suffer from pain.[69, 71, 73, 74] Brachial plexus avulsion pain is highly characteristic. It usually arises immediately or within the first days after the trauma and it tends to persist for months and years after the triggering lesion.[75-77] Patients typically complain of two types of unbearable pain.[10, 76] First, a continuous, crushing, burning, and compressing pain localized in the insensitive hand and/or in the forearm. Second, there are superimposed paroxysmal bursts of extremely severe pain shooting into the territory of the injured nerve distribution. These intermittent pains last a few seconds and appear with a high frequency during the day.[10, 76] Elapsing factors such as cold weather, illness, emotional disturbances, and depression worsen pain, while a proper distraction at work or recreation can relieve it.[10] The intensity of pain after brachial plexus avulsion injury and prior to surgical treatment depends on the extent of nerve injury.[78] Particularly, severity of pain is proved to be related to the number of spinal avulsed roots.[78]

The classical theory for the physiopathology of this neuropathic pain refers to central pain due to root avulsion and spinal cord deafferentation.[73, 77, 79, 80] Sudden nerve rootlets avulsion involves interruption of afferent pathways and degeneration of the central projections of cells in the dorsal root ganglion, resulting in a loss of sensory afferent input into the spinal cord. Consequent cellular and neurochemical changes cause disinhibition of neurons within the substantia gelatinosa and the generation of abnormal activity of neurones in the laminae I, II, and V of the dorsal horn, which fire spontaneously.[73, 76, 81, 82] Constant pain seems to be related to spontaneous aberrant activity of the neurons in the denervated posterior horn. Moreover, sudden outbursts of ectopic electrical activity in the injured part of the dorsal horn lead to convulsive pain. This neuronal hyperexcitability was shown to be gradually transmitted rostrally, with spontaneous impulses found in neurons in the Lateral Ventral Posterior nucleus of the thalamus, and in the medial thalamus.[10] Thus, a central sensitization develops as a form of pathological plasticity of the Central Nervous System.[83, 84]

Furthermore, inflammatory processes play a role in the pathophysiology of neuropathic pain. After peripheral and central nerve lesions, activation of macrophages into the nerve and dorsal root ganglion and of microglia within the CNS is responsible for the release of immune modulators. Proinflammatory cytokines as tumour necrosis factor-α and neurotrophic factors are shown to be involved in the onset and maintenance of the long-lasting neuropathic pain behavior in animal models of brachial plexus avulsion.[83, 85, 86]

Recently, an alternative hypothesis has been proposed. Based on previous data, Bertelli *et al*. estimated that in almost 80% of patients with total palsy of the brachial plexus there is at least one root not avulsed which is available for grafting.[87, 88] Furthermore, they considered that pain quickly subsided after early surgical repair by root grafting, and continuous significant amelioration of pain was noticed over the following months and years after surgery. In addition, pain relief was not related to the number

of avulsed roots. In patients with chronic palsies and persistent pain despite surgery, they found that pain was temporarily alleviated by anesthetics injection close to the non-avulsed roots. Transient pain relief *via* anesthetic neural blocks is highly suggestive of pain arising within the peripheral nervous system. Based on these observations, Bertelli *et al*. raised the hypothesis that brachial plexus pain is maybe due to the presence of a non-avulsed ruptured root rather than avulsion and spinal cord deafferentation.[88, 89] That is, in patients with subacute and chronic complete brachial plexus palsy pain arises from a preserved root or radicular remnants which remain in contact with the spinal cord and are immersed into an adverse microenvironment. After trauma, local inflammatory processes and release of neurotrophic factors contribute to pain development and force the axons to regenerate into a scar tissue. Eventually there is a neuroma formation. Therefore, root section/neuroma resection would account for early pain relief after surgery before nerve regeneration and end-organ contact. Furthermore, root grafting would create a healthy tissue where root stumps are relocated, thus preventing the recurrence of neuroma. Successful regrowth of axons and gradual remyelination of the regenerating fibers would then contribute to continual improvement of pain over time. Conversely, a large release of neurotrophic factors seems to be the cause of pain persistence in that minority of patients suffering from chronic pain despite grafting.[71, 86] Neurotrophic factors should promote nerve regeneration of axons reaching end organs in the periphery. However, because of the wide distance and time required, neurotrophic factors' secondary painful effect may prevail. Otherwise aberrant reinnervation and misdirected sensory axons regenerating in muscles are further possible explanations suggested for chronic pain after brachial plexus grafting.

Whatever the actual origin of pain, of interest is that chronic neuropathic pain rarely appears in children after brachial plexus birth injuries.[90] Neuropathic pain generally does not affect the pediatric population.[91] This considerable difference from adults likely derives from higher plasticity of both the central and peripheral nervous system throughout early development in the neonatal period and at the youngest ages. In particular, after spinal root avulsion injury and nerve trauma, rapid and efficient changes in the young nervous system allow a better recovery and an increased ability to regain function, with lower chance of developing pain.[91] Several mechanisms are proposed to explain differences between children and adults. Enhanced nerve regeneration, a distinct inflammatory response and scar tissue maturation, delayed maturation of injured fibers and peripheral nerves, neuronal plasticity, highly rich synaptogenesis, and long-lasting cortical reorganization may account for chronic neuropathic pain absence in children with OBPP.[10, 88, 90, 91] In children, lack of long-term pain behavior goes together with excellent restoration of sensory function in avulsed spinal root dermatomes and normal pain sensation reported to external stimuli in unaffected regions. All these elements support the evidence of exquisite CNS plasticity during development.[90, 92]

Somatosensory deficit

After BPI, somatosensory afference plays an important role on functional recovery of the upper limb, and in particular of the hand.[93]

In the following section we focus on clinical features of sensory deficits, on sensory testing, neurophysiological changes, sensory recovery and treatment after nerve injury.

Changes in dermatomeric representation

After BPI, the extent of sensory impairment on the upper limb generally depends on which roots have been involved, with an area of sensory deficit which follows dermatomeric distribution, both in adults,[94] and in children.[95] However, some studies in adults and infants showed how segmental sensory innervation presented peculiar characteristics which did not correspond to classic dermatomeric representation.[96] Bertelli *et al*. evaluated the distribution of sensory disturbance in 150 adult patients with brachial plexus root injury matching clinical evaluations of upper limb sensation, CT myelo-scans and surgical observations.[88] They found out that topography of sensory disturbance did not correspond perfectly to common dermatomeric distribution, possibly due to an overlapping of cutaneous innervation of the radial side of the hand. For instance, after C5-C6 root injury, disturbance in touch perception was localized to the lateral side of the forearm and to deltoid area and when C7 and C8 were also affected hand sensation was some-

what partially preserved.[88] In classical dermatomeric distribution, sensory innervation of hand is provided by C6, C7 and C8 roots. C6 distribution interests thumb and radial side of hand; C7 distribution involves second, third finger and central area of hand; finally C8 distribution reaches fifth finger and ulnar area of hand. Consequently, after C6 to C8 lesion, a complete hand anesthesia would be expected.[97]

Colon *et al*. examined sensory function using somatosensory evoked potentials (SEPs) three to seven months after birth in children with upper (C5-C7) OBPP.[96] They stimulated the thumb and the third digit and demonstrated how sensory innervation of the hand was more extensive than they expected, with alternative nervous pathways implied in the conduction of sensory sensations (*i.e.*, sensory inputs from the third digit, normally vehiculated by C7 root, were transmitted by C6 or C8 roots).[96]

Clinical features

Patients with BPI at times present "indirected clinical signs" of sensory impairment or failure of restoration of sensation. Self mutilation, finger biting and poor use of the hand, even when the motor function was preserved, were found in children with somatosensory deficit due to OBPP.[98, 99] In adult patients with sensory deficit, skin lesions and infections were noticed more commonly in the ulnar side of the hand and in the tip of the little finger (C7-T1 roots). These cutaneous areas resulted more susceptible to injury because often scraped against damaging surfaces during hand manipulation.[100]

Referred sensations

Besides sensory loss, adults with BPI sometimes develop referred sensation experience.[76, 99]

Htut *et al*. divided referred sensation into main two categories, the "right way", when sensation was "referred from the affected arm to the original source of the donor nerve afferent fibers" and the "wrong way," when sensation was referred "from a region that was not to a source of re-directed donor nerve fibers" (*e.g.*, referral sensation in the affected arm when the patient is shaving or drinking something cold).[76] In this study 56% of patients with BPI developed referred sensation at some time after injury.

This phenomenon generally decreased over time becoming stationary or completely disappearing. Only in a small group (20% of patients) referred sensation became stronger or did not change at all.

Furthermore, a different temporal "right-way" and "wrong-way" referred sensation onset was recorded. While the "right way" occurred at least six months after injury, the "wrong-way" was found at early stages from injury (in the first six months).

A lack of central plasticity and a successful peripheral nerve regeneration could explain the "right way" type. On the other hand, the "wrong way" referred sensation may be explained by the CNS reorganization after deafferentation. Since face, trunk and hand are represented in adjacent cortical areas, a dorsal root ganglia or column injury could result in an expansion of input from face and trunk areas to the hand cortical territory.[76]

On the contrary, in children a perfect localization of restored sensation routed via nerves transposed from other anatomical sites (no referred sensation experience), demonstrating evidence of exquisite CNS plasticity.[90]

Sensory examination

Although sensory deficit in infants with OBPP is difficult to ascertain,[98] response to touch and painful stimuli in newborns with OBPP and pinprick sensation in very young children could be useful to assess sensory conduction integrity.[95, 98]

In previous studies, standardized tests are used to evaluate sensory function and thresholds in children and adults:

Evaluation of pain and touch sensation, with pinprick and with cotton wool, respectively. Presence or absence of each stimulus perception is recorded (the site of these tests follow specific dermatomes as established by the Medical Research Council UK memorandum in 1976).[76, 90, 101]

Joint position sense: proprioceptive sensation is evaluated at different levels (hand, wrist, elbow and shoulder).[76, 90]

Two point discrimination test (2-PD): defined as the distance necessary to feel two contacts.[100-103] A distance of 3 mm between the points on the fingers is considered appropriate for normal levels of sensibility.[92] Pressure administrated is not standardized and children sometimes demonstrated difficulties in understanding the principle of 2-PD.[102]

Cutaneous pressure threshold: Semmen-Weinstein monofilament testing is used for the determination

of cutaneus pressure threshold.[104] Monofilaments are numbered from 1.65 to 6.65 and are placed on the skin with a pressure just adequate to bend the filament.[103] Abnormal values are considered as >no.3 monofilaments (0.0479 g) for adults and children.[76, 90, 100, 103] Filament 2.83 has been found to be a good predictor of normal pressure sensation on most areas of the human body.[102]

Vibration perception threshold: tested with a tuning fork or a biothensiometer placed on bony prominences (proximal interphalageal joint, ulnar or radial styloid process and elbow) of the investigated arm. When a tuning fork is used, the perception of vibration is assessed for 30-, 128-, and 256-cycles/second stimuli.[103] For the biothensiometer evaluation abnormal values are considered >8 V for children and >10 V for adults.[76, 90, 101]

Thermal threshold: cold and warm sensations are evaluated from a baseline temperature (*e.g.*, 30°-32 °C) and the threshold of painful cold and warm are recorded. Normal threshold values in adults are 2.5 °C for cold sensation and 3 °C for warm sensation from the baseline.[92] Abnormal values are considered in some studies as >3.9 °C for warm sensation and >2.6 °C and for cold sensation in adults aged 20-30 years (children: >3.8 °C and > 2.3 °C for warm and cold sensation, respectively).[76, 90] Hattori *et al*. tested the perception of warmth using a steel bar warmed in 50°C hot water and asking the patients if the stimulus applied is perceived.[103]

Some studies [96, 98, 105] used Somatosensory Evoked Potentials (SEPs) for the assessment of integrity of sensory conduction from the periphery to CNS in children with OBPP.

Neurophysiological changes

Clinical evidences have demonstrated the presence of sensory disturbances and an anomalous distribution of touch perception in the upper limbs of patients with BPI. This is thought to be related to somatosensory system modifications after deafferentation.[76]

To our knowledge no neurophysiological data concerning neuroplasticity or cortical reorganization after BPI are available. However, some studies described cortical reorganization of hand sensory representation after distal nerve injuries (median or ulnar nerve at the wrist).[106, 107]

Lundborg [106, 107] described a rapid reorganization of the somatosensory cortical map after a peripheral nerve injury. Nerve injury at distal sites of the upper limb was considered by the CNS as sudden deafferentation with influence to cortical hand and arm representation.

After a median nerve injury, the development of a "black hole" in the somatosensory brain cortex corresponding to the median nerve projectional areas was demonstrated. As a result, the adjacent cortical areas could overlap the "black hole" in a few minutes; this phenomenon was probably due to unmasking synaptic connection normally inhibited.

If Schwann cell tubes were preserved after a traumatic nerve injury, axons re-innerved the original peripheral target and the cortical map was exactly restored. On the contrary, a reorganization of the cortical hand map was found after a complete nerve transection followed by surgical repair. Even if microsurgical techniques have been refined with time, after nerve repair an axonal misdirection appeared.[93] This misdirection caused a mismatched reinnervation of cutaneous areas by axons growing; this phenomenon was followed by a synaptic reorganization of the somatosensory representation areas of hand and upper limb with overlapped cortical zones, like a "mosaic".[107]

Synaptic changes occurred also in subcortical sites as such as the dorsal horn of spinal tract, cuneate and gracile nuclei in brainstem, ventroposterolateral and ventroposteralmedial nuclei of thalamus, according to somatosensory afferent ways.[106]

Altered sensory perception could be also explained by modifications in physiology and biochemistry both after distal and proximal pheripheral nerve injury [107-109] with a shift in metabolism of neuronal cell body from a stance status to a growth one. In association with Wallerian degeneration, Schawnn cells started to product growth factors (INGF, CTNF, BDNF, NT3, NT4/5 and NT5-6).

Apoptosis of a large number of sensory neurons at the dorsal root ganglia was described after peripheral nerve injury and the amount of cellular loss seemed to correlate with a poor functional recovery.

A correlation was also found between sensory cell loss and the level of injury along the nerve with more proximal injuries causing a wider loss of neurons.

Cellular loss started immediately after a nerve axotomy with a great amount of death sensory cells in

dorsal root ganglia at one week and a value of 35-40% of total cell bodies reached at two months after injury.[109] Neural survival is essential for regeneration and an early surgical repair is recommended. When surgical treatment is not possible, pharmacological approaches with neuroprotective molecules could be useful.[109]

Sensory recovery after injury and surgical repair

After evaluation, sensory recovery could be classified into 8 grades using the Highet Scale.[101, 103]

Sensory recovery after BPI appears generally quite poor. Htut *et al.* evaluated sensory recovery in 76 patients with traumatic BPI before and after surgical treatment. They found a very poor sensory recovery in most patients (with or without surgical repair), with altered stimuli localization. Only the C5 dermatome had a better recovery for thermal sensation, probably due to nerve sprouting from overlapping adjacent dermatomeric areas.[76]

Similar results were found by Hattori *et al.*[103] They investigated sensory recovery of the hand after intercostal nerve transfer to median or ulnar nerve in 17 patients following complete avulsion of the brachial plexus. According to the Highet scale, they recorded recovery of superficial touch and pain sensation with some over-response (S2+) in two patients, nine patients recovery of superficial touch and pain in nine patients (S2) and recovery of deep cutaneous pain sensibility and autonomous activity of the nerve (S1) in six patients.

Hattori *et al.* (2008) found that patients with a shorter interval from injury to surgery obtained better sensory recovery, however no statistical correlation resulted between time elapsed before surgical intervention and the score on the Highet Scale.[103]

Most studies on children with OBPP examined motor recovery, however data about somatosensory function are scant.[90]

Palmgren *et al.* evaluated sensory changes in 95 patients with OBPP (14 surgically operated) and found a good recovery of sensation in the hand of the affected limb. An altered fine perception (Semmer-Weisten monofilaments test) on the affected hand was recorded in only 11% of children with upper OBPP while rates of children with sensory impairments increased (26% to 33%) when the middle and lower plexus were involved.[102]

Anand *et al.* demonstrated exquisite sensory recovery in patients with OBPP surgically operated, with good localization of restored sensation.[90] However, children who were non-operated did not show significant sensory recovery. On the contrary, Strombeck *et al.* found no differences in recovery of sensation of the hand in operated and non-operated children with OBPP when testing two point discrimination (2-PD).[105] Similar results were found by Palmgren *et al.*, suggesting that surgery does not improve sensory recovery of the hand after OBPP.[102]

Furthermore, Strombeck *et al.*, showed in 70 patients with OBPP that sensory loss is less severe than motor impairment.[92] Among the various sensory modalities, discriminative sensibility appeared the most impaired, while the thermal sensibility showed the best recovery. Strombeck [105] and Smith [110] showed how children with total palsy presented normal hand protective sensation but impairments with 2-PD.

Even though children with OBPP apparently showed a better sensory recovery than adults, this improvement after nerve graft appeared slower, considering the distance through which the axons must grow. Sensory recovery, in particular nociception, in some cases was not seen until the age of 5 years in children. The slowness of sensory recovery in infants could be attributed to delayed maturation of peripheral nerve injuries, such as at the nodes of Ranvier.[90]

Learned non-use and developmental disregard

Before sensory recovery a phenomenon termed learned non-use (LNU) in adults and developmental disregard in children could occur.

Learned non use is a concept developed by Taub *et al.* in 1976.[111] They studied monkeys with loss of sensory perception after deafferentation. As a consequence of sensory deprivation, they found impairments in motor control, even when monkeys preserved muscle strength and visual-related control of movement in the affected limb. It was observed that, after deafferentation, monkeys commonly did not use their insensate limb in spontaneous activities and restriction of the healthy forearm, associated with a training period for the insensate limb, enabled monkeys to restart using their affected limb. Subsequently, the LNU theory was generalized in humans after a CNS injury, in particular in stroke patients.[111]

The LNU basis consisted in the fact that motor deficit, resulting from injury of the CNS, is "the result not of the damage *per se* but of a learning phenomenon stemming from the damage, but whose core is the learned suppression of movement".[111]

The LNU theory was described as a consequence of reciprocally connected behavioural phenomena.

In the early period after a CNS injury, a reduced response of motor neurons resulted in a poor ability in performing functional movements with the affected limb. The repetitive failures during the use of the affected limb induced the subject to attempt different motor strategies with a preference of the non-affected limb during the execution of daily activities. Achievements in motor skills encouraged the individual to use more the unaffected limb, while excluding the affected one (Figure 1).[112]

A peculiar type of LNU phenomenon was found even in children with CNS injury (occurred in prenatal, perinatal o early-postnatal period), named developmental disregard by Taub *et al.* in 2004 and defined as a "special case of learned non-use". This phenomenon presented the peculiarity that motor activities (that in adults are lost after a CNS injury) were never experienced by children so they did not lose a function but disregarded the affected limb during their growth, while the motor function developed.[112] In this critical period, children learned strategies for the use of the non-affected limb during the execution of daily activities, discovering that tasks were easier using only the non-impaired arm.[113]

Sometimes children are unable to move the affected upper limb, even after reinnervation occurs. One possible explanation of this clinical finding is that at the onset of brachial plexus palsy there is a temporary interruption in peripheral nerves which impairs normal motor patterning and organization of body schema. So there could be a critical time after which lesions cannot cause long lasting damage and complete recovery can occur. A study by Zalis *et al.* examined 29 rabbits from birth to about one year of age. Temporary sciatic nerve interruption, by means of section followed by primary anastomosis or alcohol injections or nerve crushing, was performed at three different times: at birth, at two months and in adulthood. Recovery was very poor when nerve interruption occurred at birth, whereas it was better when nerve interruption was performed at later stages. In all three groups there was evidence of anatomic reconstitution (normal muscular endplates, normal anterior horn cells, good axis cylinders) and functional recovery (disappearance of fibrillation potentials and normal conduction velocity). This can suggest that a critical period of time is crucial to

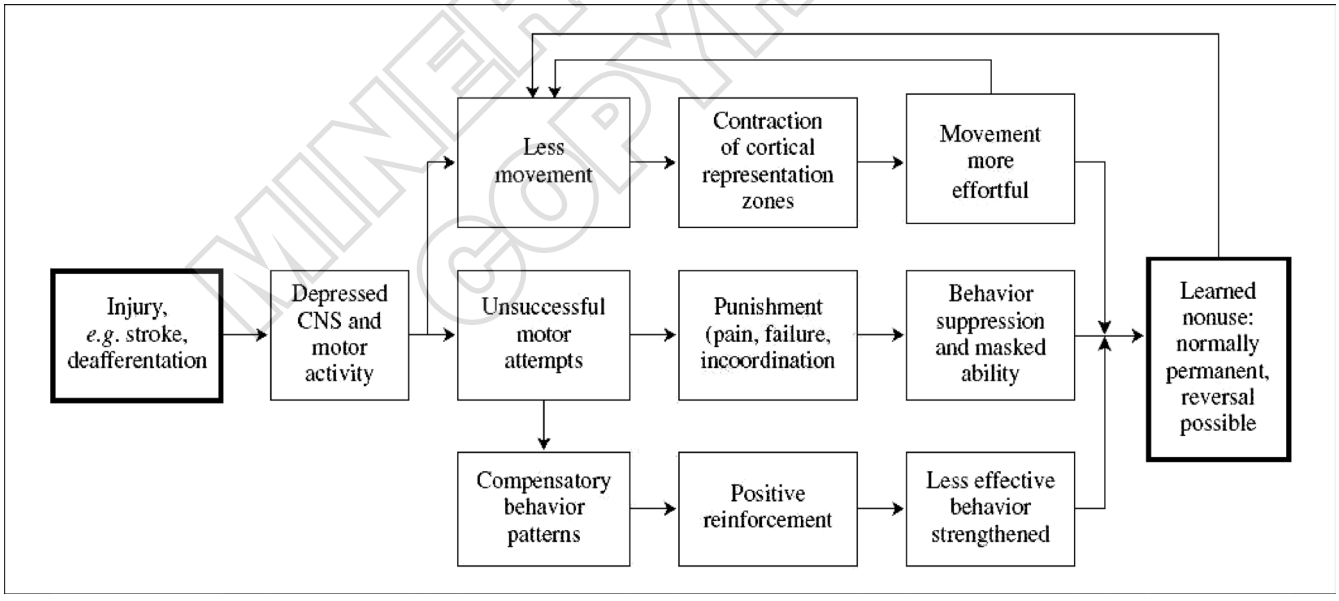

Figure 1.—Learned non-use theory (Taub 2006).

develop motor programming which can be severely impaired in case of a lack of peripheral sensory – motor inputs.[114] Brown *et al.* observed consistent findings in a study on 16 children with OBPP.[115] In patients with persistent disability, they found the presence of significant weakness and clumsiness in the affected arm despite an adequate muscle reinnervation. They hypothesized that the reduction of motor skills in the affected arm was not due only to poor nerve regeneration but was a result of inability to recruit motor units. They interpreted this phenomenon like a form of developmental apraxia. During the first months after birth, healthy children generally changed their ability in the execution of a reaching movement, from an inaccurate and afinalistic form to a more precise and visual-guided one. Arm paralysis in this critical period, in association with a lack of sensory inputs from upper limb muscles, joint and skin, led to a failure of motor areas of CNS in construction of a motor program.

Secondary deformities

During growth children affected by OBPP are at risk for the development of muscle contractures [24] and imbalance between agonist and antagonist.[116] As a consequence, a dysfunctional limb and deformities of bones and joints are frequently reported.

As regards muscular imbalance and contractures, they are probably caused by the combination of rapid limb growth and asymmetry in the degrees of nerve involvement. Healthy muscle groups are not counterbalanced and this leads to a further limitation in range of motion and to an abnormal pattern of movement of the upper limb. In particular, as a consequence of co-contractions and contractures, one of the most frequent pattern is characterized by an increased pronation of the forearm along with restricted abduction and elbow flexion, and to typical posture of the arms with the shoulder abducted, flexed elbow and forearm pronated.[116] Muscular imbalance can also arise between paralyzed external rotators (injury to the suprascapular nerve) and the strong group of internal rotators thus leading to upper limb limitation of shoulder range of motion.

As to contractures, a common pattern consists of severe medial upper limb rotation contracture; the acromion is pressed down on the humeral head causing limitations of shoulder movements and more inadequate hand function than patients without internal rotation contracture.[117] Furthermore, these children have a higher risk of developing a dysfunctional limb.[118]

With regard to deformities, children with OBPP can develop an increased retroversion of the humeral head and adaptive changes of the glenoid (glenohumeral dysplasia) [119] with permanent disturbance of joint growth and instability.[69] Another frequent bony abnormality is the scapular hypoplasia, elevation, and rotation deformity (SHEAR) which is defined as the extension and elevation of the scapula above the clavicle. It usually occurs in severe impairment of the C5 nerve root, which supplies all muscles that stabilize the scapula. In this case, the unusual inclination of the acromioclavicular joint displaces the humeral head from the glenoid fossa.[120, 121] Radiological examination can objectively detect this condition by using three-dimensional computerized tomography.[121] Other common deformities can involve both the elbow and the hand. Elbow deformities consist of angulation (secondary to an abducted and medially rotated shoulder), loss of supination (secondary to C6 root injury and weakness of the biceps muscle), shortened arm and anterior luxation of the radial head. Hand deformities are represented by abnormalities of the metacarpophalangeal joints of the 2nd through 5th fingers called the "claw hand deformity".

Rehabilitation of brachial plexus injury

Adult patients with brachial plexus palsy require early and prolonged rehabilitation treatment. It is important to try to avoid range of motion limitations, muscular contractures, stiffness of the joints and the development of secondary deformities. Physiotherapists and physicians should provide appropriate information to patients since their compliance to treatment can be crucial to achieve planned goals.

It is important not to overlook a patient's psychological status, as psychological treatment should be carried out in case of depression or associated head injury. As to patients' return to work, occupational therapists can try to improve a patient's functional ability by simulating the workplace setting and by means of adaptations or orthoses.[122]

The main goals in the rehabilitation of BPIs are prevention of muscle atrophy, prevention and restraint of secondary deformities, pain suppression,

recovery of somato-sensory deficits, developmental disregard restraint, and postoperative care.

Muscle atrophy

Development of muscular atrophy in patients with BPI leads to muscle imbalance and secondary deformities of the upper limb. Moreover, the temporal progression of structural and neurophysiological alterations in muscles after denervation is a considerable matter while nervous regeneration is occurring after a lesion. That is, considering the wide distance and time required for reinnervation, a fundamental goal in rehabilitation of brachial plexus palsy is to maintain adequate muscle trophism until the nerve reaches periphery.

A first approach to limit atrophy development is passive muscle stretching. Histochemical analysis on rats'muscles showed that the cross-sectional area of denervated soleus muscle fibers after repetitive stretching was significantly larger than the controls.[123] Stretch is an important mechanical signal acting on the production of more actin and myosin filaments and on the addition of new sarcomeres. Stretch-related mechanical loading of the muscle acts through upregulation of the signal pathway ending in the transcription of the appropriate genes.[124]

Another therapeutic approach is electrical stimulation (ES). Electrical stimulation can be applied either to the injured nerve or to the denervated muscle, both having effects on muscular plasticity and on nerve regeneration and reinnervation.[125] If an intensive daily regimen of ES is initiated as soon as possible after injury, a substantial recovery of denervated muscle size and function can be achieved, with significant improvement in wet weight, cross-sectional area, tetanic tension, shortening velocity, and power.[68, 126] The most effective stimulation method and timing are still open to question in rehabilitation, and there is no standardized program of stimulation. Comparisons between low (< 20 Hz) and high (40<Hz<100) frequency showed that the level of stimulation needed to restore muscle mass and counteract muscular atrophy, fibrosis and fat deposition is relatively low[68,127]. Biphasic rectangular long-lasting (120 ms) current pulses were necessary to recruit fibers and increase excitability throughout denervated muscles, which become less responsive even to direct stimulation.[126]

Electrical stimulation through subcutaneous impulse generator with intramuscular electrodes displays was proposed with promising results. Implantable systems would allow continuous muscle stimulation for extended periods thus improving functional results.[128]

After continuous intensive ES, a satisfactory regeneration of the severed nerve was also noted at the clinical examination and during electromyographic studies.[128, 129] Conversely, others believe that ES may be not only ineffective but may even inhibit the repair process if not properly used in terms of stimulation protocol and time of application.[125] A decreased muscle excitability and accentuated muscle fiber atrophy was observed in crushed nerve animal models, maybe due to an inhibition in release of growth factors next to nervous terminations and a suppression of terminal sprouting and reinnervation.[125] Thus, the effectiveness of very early muscle ES on injured nerve regeneration and reinnervation remains open to question.

Finally, animal and human studies tested a technique involving short-term low-frequency electrical stimulation (ESTIM) of proximal peripheral nerve stumps.[130] In rats, ESTIM at the experimental conditions (1 h, 20 Hz, 0.3 mA) was sufficient to accelerate long-distance regeneration and myelination of motor and sensory axons, especially in combination with nerve autotransplantation.[130]

In conclusion, ES could be worth starting as soon as possible and performed many times a day. The gold-standard for treatment would be the availability of home-based or portable equipments.

Management of pain

Neuropathic pain after BPI is a considerable concern in adult patients, because pain can be very debilitating and resistant to treatment. Patients with intractable pain usually have poor outcomes and a compromised quality of life. Moreover, pain is a major obstacle in rehabilitation. Another critical point is that there are no sufficient and conclusive data regarding the effects of various pain treatments in patients with a brachial plexus lesion. An adequate treatment for neuropathic pain is still needed, as pain management is a primary goal in the therapeutic approach to adult patients with BPI.

A multidisciplinary team management is advocated in these patients.[36]

First of all, a crucial role is played by early exploration and reconstruction of the brachial plexus, which is imperative not only for functional improvement of the arm, but also for the treatment of neuropathic pain.[71, 78, 131] Pain relief following successful surgical nerve repair has been widely reported,[131-133] with a better and prompter resolution compared to patients who did not undergo to nerve repair.[74, 76, 78, 134] Pain amelioration has been related to motor and/or sensory recovery, with pain improvement preceding recovery of cutaneous sensation and palsy.[74, 78, 90, 132, 131] The mechanisms at the basis of pain relief after surgical nerve repair are undefined. Successful regeneration of nerve fibres in muscle, with peripheral reinnervation by both efferent and afferent fibers are likely involved in pain reduction. End organ contacts with restoration of peripheral inputs from muscle, and/or central connections seem to contribute to modulation of pain in the spinal cord or at higher levels.[76, 78, 88] Furthermore, a good recovery would reflect the successful treatment of neuroma in a ruptured root.[88] Another significant correlation was found between the delay before nerve repair and the improvement of neuropathic pain. A shorter interval between injury and surgical repair led to a better functional outcome and higher improvement of pain.[69, 131] Kato N. *et al*. added several possible explanations for these results. First, nerve transfer may inhibit abnormal electrical activity within the substantia gelatinosa. Second, surgical intervention could have a non-specific effect depending on anaesthetic and analgesics used, or on suggestion alone. Third, sectioning of functioning axons of the posterior root system, which impulses may have been reaching the CNS, could contribute to pain relief.[131] Moreover, patients with chronic lesions undergoing late surgical repair, despite initial pain relief, have a strong chance of recurrence and have a poorer outcome, maybe due to the diminished capacity of nervous regeneration among chronically damaged neurons.[88] Of importance is also the fact that pain relief after surgery allows for early upper limb rehabilitation and therefore for a better prognosis.[131]

Pharmacotherapy is another cornerstone of neuropathic pain treatment in many pathological conditions. However, a considerable matter is the almost absolute lack of data on drug therapy in patients with BPI. Thus, a pharmacological approach is worth trying, employing different drug regimens based on evidences extrapolated from clinical trials conducted for other neuropathic pain disorders.[135] Most recent international guidelines recommend that in clinical practice the choice for chronic neuropathic pain should be made between tricyclic antidepressant and gabapentin or pregabalin as first-line treatment, while opioid analgesics and tramadol are second- or third-line options.[136, 137] Another possibility could be the combination of two or more medications, in an attempt to achieve either an additive beneficial effect or a reduction in the adverse effects. Yet, a major concern regards resistance to treatment for conditions involving central pain compared to peripheral neuropathic pain. This could be the case of brachial plexus avulsion pain. The anticonvulsant medicine gabapentin was reported to be ineffective in traumatic neuropathic pain.[138] Moreover, in anecdotal observations high doses of gabapentin for long periods before brachial plexus reconstruction were found to be related to poorer outcomes, because of a possible suppressant effect on nerve regeneration.[134] Cannabis-based medicines were tested for treatment of chronic pain associated with brachial plexus root avulsion, showing an improvement in pain severity, pain related quality of life, and measures of sleep.[139] When shooting pains are prevalent, they could be alleviated by anticonvulsivants such as carbamazepine, phenytoin, and sodium valproate.[10]

Extensive physical therapy, delivered as part of an individual rehabilitation program, is indicated among the first-line treatments to prevent pain or to alleviate it by creating an appropriate distraction.[10, 131, 135] It has been shown that a rehabilitation approach aimed at returning the patient back to work and recreation activities as soon as possible is effective in distracting patients from pain.[10, 131] Physical therapy in addition to use of orthoses is also necessary in preventing development of secondary contractures.

Transcutaneous electrical nerve stimulation (TENS) has been applied in several painful conditions, as it is a simple, cheap, and non-invasive analgesic intervention.[140, 141] However, real effectiveness is still inconclusive for chronic and neuropathic pain.[142, 143] Furthermore, in patients with BPI, this technique is conceptually adequate only for postganglionic lesions or in cases in which there is preservation of some fibers.[10] That is, at the basis of TENS effect there is the "gate control" theory of pain. Hence, nerve stimulation could not work if the

fibers of the dorsal columns are degenerated or ruptured, as in cases of avulsion injuries. The selection of parameters combinations (intensity, frequency, and stimulations site) and type of experimental pain model are fundamental in achieving hypoalgesic effects, with moderate evidence of efficacy for intense TENS.[144] Considering the favourable benefit to risk ratio, TENS is still a therapeutic option in patients with neuropathic pain.[145]

Psychosocial intervention is another important feature of a therapeutic approach for patients with brachial plexus lesions. Patients who returned to work showed greater pain relief. Even patients who did not experience pain amelioration after surgery found their pain alleviated shortly after their return to work. These observations suggest that psychological factors are important.[131]

In cases of patients refractory to more conservative treatment, interventional management is considered as a second-line option. Several neurostimulation interventions have been applied showing variable levels of evidence.[83, 135] Spinal cord stimulation (SCS) produced positive results in several neuropathic pain conditions, in particular for those characterized by complete de-afferentation. Methods of cortical stimulation including epidural motor cortex stimulation (MCS), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) were proposed as emerging alternatives for chronic medically-refractory pain disorders.[146] These techniques are based on different types of delivery of electric current to specific cortical areas of the brain, thus inducing excitability modification of neuronal activity within the neural circuits responsible for pain processing and perception.[146] In particular, DBS currently appears to be effective for pain resulting from brachial avulsion with long-term success.[147-149] MCS is a quite expensive invasive technique, with the major benefits of a prolonged duration of stimulation (hours a day for years) and positive effects on de-afferentation pain.[146, 150] rTMS is a non-invasive similarly excellent technique, while tDCS offers a less focal method of brain stimulation, being easier to apply and having low risks.[146] A recent Cochrane review states that there is insufficient and conflicting evidence regarding the efficacy of rTMS and tDCS for the treatment of chronic pain.[151]

The neurosurgical procedures for coagulation lesioning in the dorsal root entry zone (DREZ) are valuable treatment options which can be considered. The DREZ procedure involves surgical interruption of the afferent sensory input into the spinal cord, by lesioning the medial portion of the dorsal root, the Lissauer's tract, and the posterior horn of the spinal cord,[152] at a level depending on the location of the radicular avulsion. The DREZ region is an important centre of integration of painful stimuli, where paroxysmal neuronal hyperactivity might be the physiopathological basis of deafferentation pain.[153] The DREZ procedure has demonstrated good outcomes with significant pain improvement in the treatment of intractable deafferentation pain after brachial plexus avulsion.[154-157] In particular, DREZ appeared to be more effective on the paroxysmal component than on the continuous component of pain.[158]

Sensory re-education

In normal subjects, sensory impulses affering form the hand reach the cortex and thus are associated with previous memories and experiences, turning into conscious perception. After a peripheral nerve injury and nerve repair, altered profiles of neural impulses are elicited and not matched with previous experiences in the association cortex: the experience is not recognized and can result as new or pass unnoticed.[93]

Some studies have examined the effect of sensory re-education (SR) after peripheral nerve injury, concentrating particularly on distal nerve lesions. Sensory re-education is based on cortical plasticity, with cortex re-mapping by experience.

Jerosch-Herold *et al.* (2011) proposed a definition of SR: *"A gradual and progressive process of reprogramming the brain through the use of cognitive learning techniques such as visualization and verbalization, the use of alternate senses such as vision or hearing and the use of graded tactile stimuli designed to maintain and/or restore sensory areas affected by nerve injury or compression to improve tactile gnosis".*[159]

Lundborg *et al.* (2007) divided SR into two temporal phases after injury. The earlier one focused on cortical hand representation maintenance using visuo-tactile (*e.g.*, mirror therapy) and audio-tactile interactions, and the later phase dedicated to enhancing sensory re-education results.[107]

While classical SR methods were designed to improve sensory function after reinnervation (later

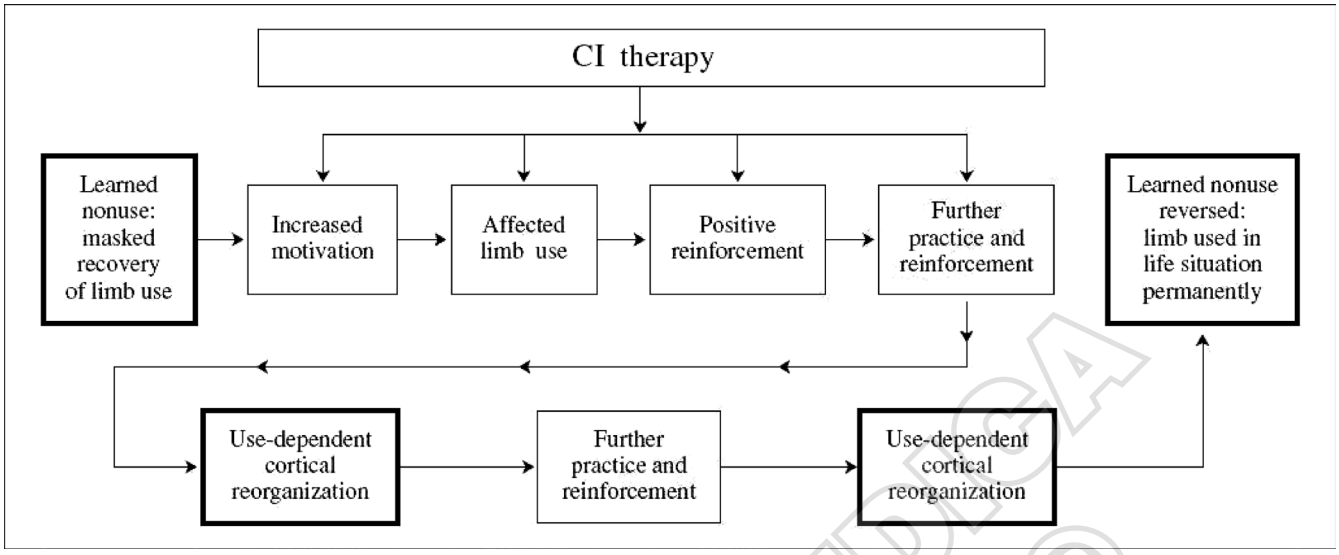

Figure 2.—CI therapy applied to LNU theory (Taub 2006).

phase), new sensory re-educational programmes were created to maintain a correct cortical reorganization (earlier phase).[159]

Exercises to regain tactile gnosis in adult patients include perceiving of different textures and shapes with eyes opened or closed, and training the capacity to localize a stimulus. Other cortical functions, such as attention and memory, are also involved during training.[93] Recently, new techniques were developed using enhanced treatments, like the "sensor glove system" [160] or selective temporary anesthesia.[108]

Oud *et al.* (2007) reviewed studies focused on the rehabilitation of sensory impairments of the hand after peripheral nerve injury and found limited evidence of the effectiveness of sensory re-education stressing the need of further clinical trials.[93]

More recently, Jerosch-Herold *et al.* (2011) reviewed re-education techniques for recovery of hand sensibility after peripheral nerve injury. They found that classical methods (retraining of tactile gnosis using different shapes, textures) were generally used more frequently than innovative techniques (mirrors and sensory substitution) developed in the last 10 years.[159]

Treatment of developmental disregard

In order to contrast LNU or developmental disregard phenomena, a targeted technique, the Constrained Induced Movement Therapy (CIMT), was developed.[161]

The goal of CIMT is to reduce the behavioural suppression of the motor activity in the impaired limb. The use of the non-affected upper limb is limited by using a glove or a sling and intensive activities of the affected one could be associated for the 90% of waking hours. In addition, a repetitive training of the affected limb for 6 hours a day for 2-3 weeks was suggested for adult patients.[162]

Modified approaches of CIMT (modified-CIMT, m-CIMT) have been proposed in order to increase the feasibility and tolerability, especially in children, by changing the type of restraint used and the frequency and intensity of intervention.[162, 163]

Studies on CIMT were initially performed on monkeys subsequently applied to humans, focusing on patients with upper limb impairment after stroke.[164, 165]

The two mechanisms proposed to explain CIMT effectiveness are changes of the behavioural approaches and the consequent cortical reorganization (Figure 2).[162]

To date, studies regarding the application of CIMT and m-CIMT in children concentrated on children with hemiplegia due to cerebral palsy,[162, 166] while only a few case reports on OBPP are available.

Smania *et al.* enrolled six children with OBPP (aged: 6-22 months) in a pilot study (unpublished

TABLE I.—*Characteristics and performance outcome measures at pre-treatment and post-treatment.*

Patient no.	Sex	Age (mo)	Affected side	Lesion level	Use test[166] (0-64)		Function test[166] (0-120)	
					Pre	Post	Pre	Post
1	F	9	R	C5-C6-C7	14	27	87	91
2	M	11	R	C5-C6	0	7	72	76
3	M	21	R	C5-C6	20	33	96	107
4	M	15	R	C5-C6	28	34	110	111
5	M	10	R	C5-C6	7	20	94	97
6	M	17	R	C5-C6	5	13	88	95

F: female; M: male; mo: months; R: right; Pre: pretreatment; post: post-treatment.

data) to evaluate the effects of a mCIMT protocol focused on reducing learned non use of the affected arm (Table I).

All children wore a cotton mitten on the unaffected hand 8 h/day for a four-week period during which they underwent to 1 hour of physiothearpy sessions (3 times a week for 4 weeks). The mitten prevented the child from grasping with the unaffected arm while bimanual tasks were allowed.

The amount of use and the functional performance before and after treatment were evaluated by means of two specific tests (use and function test).[166]

At the end of the treatment, an improvement in use of the affected arm was recorded in all patients, suggesting that the m-CIMT program could have been a promising rehabilitative procedure in children with OBPP.

Following studies confirmed these preliminary data.

Vaz *et al.*[167] studied the application of CIMT in a two year old child with difficulties in brushing hair due to OBPP; she wore clothes with a front opening and trousers with an elastic waistband. Treatment protocol lasted fourteen weeks and the healthy limb was constrained with the child's clothes (a jumper) for 30 minutes a day while the affected limb was used in gaming activities based on the child's interests. Despite the initial low tolerance to treatment, the child soon adapted to training. The difficulty of exercises gradually increased during the treatment as the child improved.

Upper limb functional outcome was assessed with the Toddler Arm Use Test before and after treatment. In addition a schedule compiled by the child's mother, after treatment, contributed to understanding the improvements in daily life activities. Results showed an increase in willingness, endurance and quality of movement. There was no follow-up assessment.

Buesch *et al.*[168] evaluated CIMT effectiveness in two 12-years old children. Treatment lasted 126 hours (three weeks for the first child and four and a half weeks for the second one). A CIMT splint was applied to the healthy arm, while the affected upper limb was involved in functional exercises (*e.g.* pulling out little objects from a jar). The outcome measures were the Melbourne Assessment of Unilateral Upper Limb Function, Nine Hole Peg Test (NHPT), and the Assisted Hand Assessment. Scores were recorded pre-treatment, post-treatment and at three weeks post treatment. Children and their parents provided a further evaluation of daily use of the impaired limb by filling in a diary. Both children improved hand functionality and finger dexterity, which remained at follow-up. An increase of functional use of the affected limb in daily activities was described only in one child.

Santamato *et al.* (2011) reported the experience of two children with Erb-Duchenne palsy. The first one was a six year old girl, who could reach objects with the affected arm but did not use it spontaneously. The second one was a seven year old girl with a major impairment of the upper limb (she did not use it at all). The treatment protocol consisted of a 30 minute session once a day for two months and the non affected limb was restrained with a jumpsuit with velcro-closure in order to minimize the irritability of children. Before mCIMT, the children were treated with intramuscular injection of botulinum toxin – A (BTX-A) into the involved upper limb (20 UI into biceps brachii at two sites and 15 UI into pectoralis muscle at two sites), in order to inhibit co-contraction and to facilitate motor control. Injections were followed by a 10 day rehabilitation programme based on muscle stretching and then the mCIMT protocol was initiated. Outcome measures used were Gilbert-Raimondi

score for elbow function, Gilbert shoulder score for shoulder movements, Raimondi Hand score and NHPT for dexterity, and Medical Research Council (MRC) for muscle strength. Patients were evaluated before treatment, after treatment and at two-month follow-up.

Results showed an improvement of extension, abduction and adduction of the affected limb, while no modification in MRC scores were found. Functional improvement persisted 6 months after the end of treatment without further injection of BTX-A and parents reported important improvements in the execution of daily activities and in bimanual tasks.

Despite these initial positive results, further studies are necessary to evaluate the effectiveness of CIMT in clinical practice, both in children with OBPP and in adults with brachial plexus injuries.

Treatment of secondary deformities and post-operative care

As to physiotherapy, at first it consists of exercises that maintain upper limb passive range of motion, then gravity – assisted exercises are carried out. As muscle strength starts to develop, resistence and the use of isokinetic machines can be introduced.

Patients generally tend to neglect injured limbs, therefore therapists and clinicians must instruct them to take care of the injured limb and avoid traumas and disuse.

Thermic hypo-anesthesia as a result of lesions can lead to the application of an abnormal amount of heat to the patient's injured limb and to potential harmful consequences for the patient. Therefore, specific care for the affected upper limb should be recommended to patients.

Upper limb passive movements and physiotherapy can be combined with orthoses, such as the whole arm flail splint, and elbow and hand splints which can contribute avoiding stiffness and range of motion impairment. The flail arm splint, for instance, is a sort of artificial upper limb that comprises a shoulder support, an elbow ratchet, a forearm support and a gauntlet part which can be attached to a number of devices applied to improve patient's function like split hook and tool holder.[170] Physiotherapists and physicians should also pay attention to the development of muscle contractures which can be painful and alter posture and function. Therapies like ultrasound and TENS, associated with a scar massage, can improve muscular contractures and prevent nerve compression.

Agonist and antagonist muscles cocontraction can cause abnormal and fixed joint positions and impair functional recovery. Biofeedback can be a useful approach [134] as well as BTX-A inoculation in the target muscles. BTX-A injection has been demonstrated to be useful in the treatment of imbalanced muscle contraction in children with OBPP. In particular BTX-A has been used in combination with other conservative treatment, such as physiotherapy, occupational therapy, CIMT and serial casting, and functional surgery for the reduction of altered posture of the affected limb.[169, 171] Furthermore, the use of BTX-A could play a role in motor control and neuroplasticity facilitation by the inhibition of muscle co-contraction.[169] Despite the available literature studies, further randomized controlled trials are recommended in order to support indications and utility about the use of BTX-A in children with OBPP.[171, 172]

As regards OBPP rehabilitation, the aim of rehabilitative treatment is the prevention of a range of motion impairment and avoidance of muscular contractures or joint dysmorphism. To achieve this it is necessary to move the affected limb cautiously early after birth. As a consequence, timing to start the treatment is still subject of debate, but a primary home program can start after 7 to 10 days after birth, and if no results are achieved after one month, an intensive treatment is needed. In particular glenohumeral joint movements and the stabilization of the scapula should be performed. To this purpose abduction and external rotation splints can be useful to maintain range of motion, but a high level of compliance by the patient is required and joint development impairment could occur.

To avoid shoulder internal rotation deformity and glenohumeral dysplasia, it is important to monitor the function of passive external rotation of the limb with adduction limitations, which is correlated with the degree of joint abnormalities, and may direct to diagnostic deepening like MRI scan, or surgical approaches. External rotator muscles strength is very important since its alteration is associated with patients' severe functional impairment.[21]

Patients who undergo surgery should be treated immediately in order to achieve long term goals. Custom made braces are built immediately after surgical treatment to keep the upper limb in abduction. Movement of the head is also limited so that nerve

coaptation can be prevented. Patients keep wearing the brace for 6-8 weeks and then use a sling. Passive stretching in external rotation should be performed to prevent secondary deformities and in particular to correct imbalance between strong arm internal rotator muscles and weak external rotators. In case of dislocation of the radial head and consequent supination of the forearm with intrinsic minus posture of the hand, correct repositioning and ligamentous reinforcement can help to reduce consequences and patient's functional impairment.[179]

When neurotization is performed patients can also practice so-called induction exercises which can help the donor nerve to fire in case the reinnervated muscle is active.[134]

Six months after the intervention the first follow-up evaluation in carried out. Tinel's sign is important to assess reinnervation progress. Indeed its advancement rate along the nerve provides important prognostic information and reflects progressive nerve regeneration. Needle electromyographic studies are also good prognostic predictors.[134]

Conclusions

The present paper is the first review of the literature on the epidemiology, classification and rehabilitation issues of BPI in both adults and children. It is worth noting that this is an exclusive paper in its field, giving clinicians important feedbacks on the existing procedures potentially useful in the management of patients with BPI.

According to the literature some major concerns must be acknowledged.

First, muscle atrophy is one of the major issues in these patients, and therefore it is one of the main goals of rehabilitation. In order to prevent and/or reduce the amount of muscle atrophy, studies on both animals and humans have shown that ES is an inexpensive, simple and effective tool in both adults and children. In particular, ES may reduce atrophy and maintain muscles until neural recovery occurs.

Future randomized control trials with large sample sizes and follow-up evaluations on both adults and children are required. In addition, it would be interesting to perform studies that use imaging (*i.e.*: MRI, US) to study how the visco-elastic muscle properties may be preserved over time due to ES.

Second, pain is one of the main challenging concerns in adults with BPI. Since it is primarily related to nerve injury, the first line therapy is represented by surgical nerve repair (when possible) and by pharmacological treatment. However, it is important to consider that pain is a multidimensional phenomenon involving both an objective (tissue damage) and subjective (perceptual, affective, cognitive and behavioral components) dimension. In addition, nociceptive/inflammatory processes may contribute to increase pain and disability. Thus, pain relief in BPI requires a multi-professional approach and a comprehensive treatment plan consisting of both physical and medical procedures. In particular, future studies are needed to evaluate the effectiveness of partially unexplored non-pharmacological approaches (*i.e.*: TENS, US, Laser therapy, acupuncture) combined with surgery and pharmacological treatments.

Finally, the effect of deafferentation of the affected limb and the learned non use behavior (in adults) or developmental disregard (in children) are frequent results in BPI. Several studies involving patients with CNS damage and preliminary studies in OBPP patients showed that a specific rehabilitation protocol, such as the CIMT protocol, might reduce these negative consequences. In particular, in children, future studies are recommended in order to evaluate the effectiveness of specific rehabilitation programs focused on promoting both recovery of function and use of the affected limb.

To conclude, research on the effectiveness of combined treatment protocols in the management of BPI is an important field of neurological rehabilitation, which is recommended for the future.

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