Intracranial nerve repair: a review of experimental and clinical studies

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With recent developments in neurosurgery and related disciplines, more aggressive approaches are being made for various lesions of the skull base, and, as a consequence, cranial nerves are more frequently damaged, which causes significant morbidity. The authors review experimental and clinical studies involving surgical repair of severed cranial nerves and provide evidence that some degree of functional regeneration occurs. Functional recovery after repair is mainly dependent on the preoperative function of the muscle-nerve unit and the morphological organization of the nerve; the more complex the organization, the lesser the degree of functional recovery. The beneficial effect of surgical repair on postoperative morbidity is outlined together with suggestions for future research.

Key Words * cranial nerve * nerve regeneration * skull base surgery * suture

Developments in neuroanesthesiology, neuroradiology, computer-assisted planning of operations, and microneurosurgery together with a better understanding of microanatomy have resulted in a more frequent and more aggressive surgical approach for complex neoplastic and vascular lesions of the skull base.[2,13,31,65,78,81,82] As a consequence, cranial nerves three to six are more frequently at risk during surgery in the cavernous sinus region, whereas cranial nerves seven to 12 can be injured during surgery in the posterior fossa region. In these surgical procedures, cranial nerves may be sacrificed for the sake of complete tumor removal or to achieve a satisfactory operative approach; nerve injuries can also occur during surgical manipulations.

For many years, the intracranial parts of the cranial nerves were thought to be unreparable. This was partly due to the technical difficulties in repairing these delicate structures as well as the belief that the cranial nerves did not regenerate. In the last decennium, several experimental and clinical studies proved the opposite. In this review, studies on intracranial nerve repair are analyzed and future developments are outlined.

ANATOMICAL AND HISTOLOGICAL CONSIDERATIONS

Although some surgical principles of peripheral nerve surgery also apply to cranial nerves, there are distinct anatomical and histological differences between the cranial and peripheral nerves.[63,84,87] Therefore, cranial nerve repair should have its own surgical concept adapted to the specific structure of the nerves and its regenerative potential. For convenience, cranial nerves will be taken to consist of those

parts of cranial nerves that are located intracranially. No results will be reported on repair of extracranial portions of the nerves. We will avoid the use of the word "anastomosis" as a term for nerve repair in this paper. Although anastomosis is frequently (but incorrectly) used in many papers on nerve repair, fundamentally, it means coaptation of a hollow structure.

Anatomical Considerations

From an anatomical point of view, the cranial nerves lie freely in the cerebrospinal fluid (CSF) throughout their length.[47,48,63,84,87] They are only fixed at the exit point from the brainstem and at the exit point of the skull. Because the cranial nerves are not subjected to movements or directly embedded in tissue, they are not adapted to stretching or any mechanical forces from outside. There is almost no surrounding tissue in close contact with the cranial nerves, implying that cranial nerves rely on direct vascularization of the supplying vessels and vessels in pia mater.[46-48]

Compared to peripheral nerves, the cell bodies of the axons of the cranial nerves are very close to the possible site of injury. Whereas in peripheral nerves the distance between injury and the cell body can be longer than 100 cm, in cranial nerves this distance is at most a few centimeters. This has serious consequences for the regenerative potential. It is known that lesions close to the cell body are accompanied by impaired regeneration.[23,37,43,58,64] The interruption of the continuity of an axon leads to characteristic changes in the various parts of the neuronal unit preparing the cell for regeneration of the cell and its distal segment.[33,73] After transection, the cell body loses its connection with a substantial part of its plasma. In the cell bodies the proteosynthesis is clearly increased. The axons by themselves possess almost no capacity to synthesize macromolecules, and thus they depend completely on the perikarya to supply these substances during the process of regeneration. The chromatolytic hypertrophic changes occurring in the cell body are more pronounced the closer the transection is made to the nerve cell.[88] The regeneration of axons in these lesions is consequently impaired because the amount of distal axon to be replaced may exceed the metabolic activity of the cell. Also, the amount of total neuron cut away and separated is larger, and thus the amount of cellular disruption is greater. Sometimes, this loss will exceed the tolerance of the neuron. The increased metabolism will be selectively used for survival of the cell body without regeneration of the distal segment.

Little is known about the effect of CSF on cranial nerve regeneration. It is likely that the CSF has a metabolic relationship with the endoneurial compartment of the nerves. Circulating hormones and other substances in the CSF could influence the nerve regeneration. Adverse effects can also be expected, such as from circulating blood products and various inflammatory cells after infection in the CSF. The local neurotrophic factors produced by the distal stump of the transected nerve may be diffused by the CSF, thus diminishing axonal outgrowth.

Histological Considerations

From a histological point of view, the cranial nerves lack an epineurial layer. They also lack a firm perineurium, and they are enveloped by only a single or double layer of flattened sheath cells without a continuous basal lamina.[48,61,62] The collagen content of cranial nerves is much less than that of peripheral nerves, and there is no interfascicular connective tissue that separates fibers into branches. Although it is believed that there is a certain degree of somatotopy in cranial nerves, there is no macroscopical fascicular organization. Also, the intracranial segments of the cranial nerves undergo a transformation in their structure at some point along their length. This transition zone, which is a wedge-shaped area extruding from the brainstem into the nerve, differentiates between central

myelination (by oligodendrocytes) and peripheral myelination (by Schwann cells).[63,84] As a consequence of these structural properties, cranial nerves are mechanically much less stable and more vulnerable to any type of surgical manipulation than peripheral nerves.

ANIMAL STUDIES

Saitoh[68] was the first to report on oculomotor nerve regeneration after surgical repair in dogs. Almost complete transection of the nerve was followed by suture repair. Eight of the 11 dogs regained nearly normal eye movement 9 months after repair. Moderate pupil constriction was noted in nine dogs and normal constriction in two. Subsequently, Sandvoss, et al.,[71] performed a series of experimental repairs of the oculomotor nerve in cats. The nerves were glued either with Aron Alpha (Japanese fibrin glue), with heterogeneous fibrin glue, or coapted with lateral slit silicone cuffs. Three months after surgery, clinical investigation, electromyography, and histological studies showed optimal regeneration in fibrin glue repairs. Aron Alpha repairs were unfavorable because of atrophy and scar adhesions. Control cats that had not undergone repair showed no signs of regeneration. This study was followed by investigations of abducens nerve repair in cats.[72] Nerves glued together with fibrin glue revealed good reinnervation within 3 months, with ideal parallel alignment of the nerve fibers at the repair site. Nerve repair using Tabotamp or Aron Alpha resulted in neuroma formation, adhesions, and atrophy of the nerve with impaired recovery. Fisch, et al.,[29] showed that facial nerve repair performed with a collagen splint avoids fibrosis and leads to minimal ingrowth of connective tissue in cats.

Groups led by Fernandez and Pallini[25-27,64] investigated nerve morphometry and functional regeneration after oculomotor nerve repair. In rats, the oculomotor nerve was sectioned and the nerve stumps were coapted with plasma clot.[26] Functional recovery of the nerve was assessed by measurements of the pupillary diameter and the ocular displacement evoked by vestibular stimulation. In the postoperative period, pupil diameter showed a progressive reduction, whereas the horizontal and vertical ocular displacements were decreased. The vestibular stimulation in the horizontal plane evoked anomalous eye movements with vertical components. The regenerated nerves showed a progressive increase of axonal diameter and myelin sheath thickness. Somatotopic organization of the motoneurons of the reinnervated muscles showed less specific, bilateral representation in the midbrain compared with normal muscles having unilateral representation. This was ascribed to a plastic response of the brainstem neurons to misdirected regrowth of axons in the distal nerve. In a study of the repair of cranial nerves three and six in rats, functional recovery of the abducens nerve was much better than that of the oculomotor nerve, suggesting that complexity of the nerve motor system organization is a major factor influencing the functional outcome.[25] In a study in guinea pigs, the effect of proximal and distal transection on oculomotor nerve regeneration was investigated.[64] The nerve was sectioned at the edge of the tentorium or at the orbital fissure and then coapted by plasma clot. After proximal repair, functional recovery varied among different animals and remained stable. In poorly regenerated nerves, aberrant eye movements were found, and the somatotopy of the neurons was greatly altered. After distal repair, extraocular motility had recovered and no aberrant eye movement was observed.

A comparative study of laser-assisted nerve repair versus fibrin glue was performed by Seifert and Stolke[75,76] in cats. The cut oculomotor nerve was either fused together with a CO₂ mW laser or coapted with fibrin glue. Regeneration (evaluated by pupil diameter measurements) was "almost complete" in four nerves and "partial" in two cats that underwent laser-assisted repair. Histomorphological examination revealed good regeneration across the laser repair without significant scarring effect or constriction at the repair site. One partial recovery and separation of two nerves was

found in fibrin glue repair.

Recently, Glasby, et al.,[32] repaired the facial nerve in the cerebellopontine angle of sheep. The transected facial nerve was repaired with freeze-thawed muscle autografts that were 5 mm in length and then coapted with fibrin glue. One year after surgery, clinical improvement of facial paralysis and a return of the corneal blink reflex were noted in five of six sheep. In one case the nerve was separated. Neurophysiological examination confirmed the return of function with nearly similar motor latencies and conduction velocity between the normal and repaired nerves. Morphological examination showed small but normally myelinated nerve fibers in the distal nerve segment.

CLINICAL STUDIES

TABLE 1 SUMMARY OF DATA ON INTRACRANIAL THIRD AND FOURTH CRANIAL NERVE REPAIR									
Authors & Year	Cranial Nerve	Type of Repair	No. of Cases	Coaptation Technique	Follow-Up Review (mos)	Oculomotor Function*			
						Excel- lent	Good	Fair	Poor
Iwabuchi, et al., 1982	III	end-to-end	1	sutures	18		1		
Grimson, et al., 1984	IV	end-to-end	1	sutures	5	1			
Deruty, et al., 1988	III	end-to-end	1	sutures†	18		1		
Ferrier, et al., 1992	IV	end-to-end	1	sutures	6	1			
Krajewski, 1992	III	graft (1 cm)	1	sutures	24		1		
Sekhar, et al., 1992	III	end-to-end	1	sutures/fibrin glue	36				1
		graft	1	fibrin glue	14			1	
	IV	end-to-end	1	sutures/fibrin glue	12			1	
	V† (Partial)	graft	3	sutures/fibrin glue	18-52			1	2
		graft	1		24			1	
	VI	end-to-end	3	sutures/fibrin glue	25-60			1	2
		graft	6	fibrin glue	21-35	1	1	3	1
Sindou, et al., 1992	IV	graft (1 cm)	1	fibrin glue	7	1			
Present study	IV	graft (0.5 cm)	1	sutures/fibrin glue	5	1			
	VI	graft (1.5 cm)	1	sutures/fibrin glue	6		1		
* Outcome according to Table 2, adapted from Sekhar, et al., 1992, and Biglan, et al., 1994.									
† Nerve repair site wrapped with Teflon sheath.									

Most articles on the repair of cranial nerves three to six consist of case reports.[15,28,34,38,44,80,83] Only Sekhar, et al., [79] published a relatively large series on cranial nerve repairs during operations for tumors in the cavernous sinus region. The data from these case reports are summarized in Table 1. The ocular motility grading system[79] for evaluation of cranial nerves three to six is given in Table 2. For the facial nerve, the published series are obviously much larger.[1,3,8,9,19-22,24,29,39-42,49,52,66,69,86,90] In some cases of cranial nerve repair, the follow-up period was relatively short. It must be stated that the continued recovery after nerve repair can proceed for 5 to 10 years after surgery, although the most significant improvement is observed within the first 2 years after surgery.

TABLE 2 OCULAR MOTILITY GRADING SYSTEM*	
Grade	Grading System
excellent	singular binocular vision in primary gaze & reading position; vision extends 20° on right, left, upward, & downward gaze
good	singular binocular vision in primary gaze & reading position but diplopia out of these gaze positions; partial ptosis
fair	diplopia in primary gaze or reading position but singular binocular vision with a specific head posture
poor	absence of singular binocular vision; poor-to-absent eye movement; complete blepharoptosis
* According to Sekhar, et al., 1992 and Biglan, et al., 1994.	

Oculomotor Nerve

Iwabuchi, et al.,[38] were the first to perform an end-to-end suture repair of the oculomotor nerve after accidental transection during surgery of a parasellar adenoma. One and one-half years after repair, adduction of the left eyeball was almost normal and the patient did not suffer from diplopia. Deruty, et al.,[15] describe repair of the oculomotor nerve after transection (several millimeters from its entry into the brainstem) during excision of a schwannoma. After 18 months, ptosis had disappeared and adduction of the eye reappeared. The patient continued to have an absent pupil reflex to light and vertical movements of the eye were restricted. Krajewski[44] repaired an oculomotor nerve that was damaged during surgery for a lateral retrosellar adenoma. The patient showed partial recovery of nerve function 2 years after surgery. Normal horizontal gaze was restored, ptosis was absent, and the pupil reacted slowly to light.

Two cases of oculomotor nerve repairs were reported in the series by Sekhar, et al.[79] In the first case, an end-to-end nerve repair was performed with sutures and fibrin glue. The functional recovery of the nerve after 36 months was partial but similar to the preoperative state. The second case was a graft repair over a distance of 3 cm using sutures and fibrin glue. After 14 months, the functional return consisted of slight pupil reaction to light, partial ptosis, and movements of the eye in all directions.

Trochlear Nerve

Grimson, et al.,[34] repaired a trochlear cranial nerve that was transected during aneurysm surgery. Within 5 months after surgery, the superior oblique palsy had resolved with full recovery of the vertical gaze of the eyes and a return of the right optic disc to its normal anatomical relationship with the fovea. Also Ferrier, et al.,[28] Sindou, et al.,[83] and van Overbeeke (unpublished results) describe complete return of trochlear nerve function after end-to-end nerve repair.

Trigeminal Nerve

Sekhar, et al.,[79] reported on four cases of trigeminal nerve repair. In three patients, the ophthalmic root was repaired with nerve grafts. The corneal reflex was complete in one patient and incomplete in another patient. The complete trigeminal nerve was partially injured in one case and consequently repaired with a nerve graft using sutures. In this patient, recovery was also partial.

Abducens Nerve

Nine cases of abducens nerve repair were described by Sekhar, et al.[79] End-to-end repair was

performed in three nerves; functional recovery was complete in one case, good in the second, and poor but similar to the preoperative state in the third case. Six nerves were reconstructed with nerve grafts. In one case with a partially injured nerve, complete recovery was attained. In three patients the recovery was partial. In two patients who underwent direct neurotization of the nerve graft (insertion of the nerve graft into the lateral rectus muscle) recovery was excellent and poor, respectively.

Facial Nerve

Because the facial nerve is quite frequently damaged during surgery for cerebellopontine angle tumors or vascular lesions such as aneurysms, vast experience in the repair of this nerve has been accumulated. Until the mid 1970s, facial paralysis that occurred in association with performing intracranial procedures was managed by nerve substitution techniques such as hypoglossal-facial coaptation or facial-spinal coaptation. Pioneered by the work of Dott[16,17] and Drake,[19-22] microsurgical techniques have permitted restoration of the facial nerve by end-to-end repair or grafting techniques. In 1936, Dott was the first to perform an intracranial-extratemporal bypass of the facial nerve with a sural graft after total removal of a large acoustic neuroma.[17] In 1960 Drake was the first to perform secondary grafting[19] and later end-to-end repair[20-22] after removal of acoustic tumors in four patients. These patients showed "gratifying recovery of facial function and especially a useful degree of emotional movement." Soon it was shown that the results of primary repair were superior to those obtained by the nerve substitution techniques.[9]

TABLE 3
SUMMARY OF DATA ON INTRACRANIAL FACIAL NERVE REPAIR

Authors & Year	Type of Repair	No. of Cases	Coaptation Technique	Follow-Up Review (mos)	Facial Nerve Function*		
					Good	Fair	Poor
Drake, 1972	end-to-end	7	sutures		4	—	3
	graft	4			3	—	1
Yasargil, et al., 1977	end-to-end	11	sutures		4	5	2
Brackmann, et al., 1978	end-to-end	7	sutures	24–84	6	—	1
	graft	2			2	—	—
Barrs, et al., 1984	end-to-end	18	sutures/Avitene	24–72	15	—	3
	graft	6			4	—	2
May, 1986	end-to-end	8	sutures	>24	7	—	1
	graft	27			14	4	9
Pluchino, et al., 1986	end-to-end	23	sutures	2–108	6	9	5
	graft	3			—	—	3
Fisch, et al., 1987	graft	8	collagen splint & fibrin glue	36–120	8	—	—
Jääskeläinen, et al., 1990	end-to-end	20	sutures	36–117	9	—	11‡
	graft	5			2	—	3‡
King, et al., 1990	graft	8	sutures/ fibrin glue	—	1	5	2
Kanzaki, et al., 1991	end-to-end	6	sutures or fibrin glue	12–144	3	—	3
	graft	3		6–46	1	—	2
Leutje, et al., 1991	end-to-end	18	sutures/Avitene	>18	7	8	3
	graft	1		>18	—	1	—
Arriaga, et al., 1992	end-to-end	14	sutures/Avitene	8–96	5	2	6
	graft	9			1	3	4
Ebersold, et al., 1992	end-to-end	7	sutures	12			
	graft	1					
Stephanian, et al., 1992	graft	22	sutures§	6–65	10	8	4
King, et al., 1993	end-to-end	6	sutures/ fibrin glue	24–108	4	—	2
	graft	12			5	2	5
Blomstedt, et al., 1994	end-to-end	6	sutures	20–118	2	1	3
NF2†	graft	2		66–68	—	1	1
non-NF2†	end-to-end	17	sutures/ fibrin glue	21–114	7	7	3
	graft	5		47–104	3	1	1
Samii & Matthies, 1994	end-to-end	17	sutures/ fibrin glue	6–94	12	5	—
	graft	27		14–126	20	5	2
total	end-to-end	185			91(49%)	37(20%)	46(25%)
	graft	145			74(51%)	30(21%)	39(27%)

* Three categories are used: good, moderate, and poor. The good grade is equivalent to Grades I, II, and III of the House–Brackmann scale, fair to Grade IV, and poor to Grades V and VI.

† After removal of Neurofibromatosis-2 acoustic neuromas; the results are presented in some cases after secondary reanastomosis procedures. Some of these patients have been reported earlier by Jääskeläinen, et al., 1990.

‡ House–Brackmann Grade IV to VI.

|| The results were presented with those achieved after preservation of the facial nerve.

§ In some cases fibrin glue was also used.

The data from large series of intracranial facial nerve repair are summarized in Table 3; most of the articles deal with acoustic neuroma surgery. Besides these series there are several single case reports on intracranial facial nerve repair after both trauma[67] and tumor removal;[18,59] all of them show that facial nerve function recovers to some degree. For interpretation of the results after facial nerve repair, a

simplified House-Brackmann[36] grading system was used as proposed by King, et al.,[42] (Table 4). Good results are obtained in approximately 50% of the patients.

TABLE 4 SIMPLIFIED HOUSE-BRACKMANN GRADING SYSTEM*	
Grade	Outcome
I: normal	normal facial function
II: mild dysfunction	minimal facial weakness or other defect sufficient to prevent classification as Grade I
III: moderate dysfunction	pronounced facial weakness irrespective of synkinesis but with complete eye closure
IV: moderately severe dysfunction	same as Grade III but without complete eye closure
V: severe dysfunction	return of tone with or without minimal muscular contraction
VI: total paralysis	complete facial paralysis: no tone or muscular contraction
* According to the system of King, et al., 1993.	

Cranial Nerves Eight, Nine, 10, 11, and 12

There are no separate reports on the intracranial repair of nerves eight, nine, 10, 11, or 12. Only Sekhar, et al.,[79] mention in their paper on temporal bone tumors repair of the glossopharyngeal, vagal, and accessory nerve in four cases using cable grafts. However, the clinical course and recovery of these repairs were not described. Matthies, et al.,[51] report on accessory nerve repair with nerve grafting after meningioma removal in the cerebellopontine angle. Nine months after surgery motor recovery had proceeded up to Grade M3 (muscle contraction against gravity).

DISCUSSION

Aggressive surgical strategies for skull base lesions will increase cranial nerve lesions. Compared to peripheral nerve surgery, intracranial nerve surgery is still an unexplored area. Although interest in cranial nerve regeneration emerged as early as 1938,[5,6] the first clinical report on intracranial nerve repair (except the facial nerve) was not published until 1982.[38] Although most of the clinical literature consists of case reports, some conclusions and recommendations can be postulated. Moreover, some basic neuropathological considerations and controversies will be outlined that should raise further points for future discussion and research.

Coaptation Technique

Because of the anatomical and histological considerations outlined earlier, operative reconstruction of cranial nerves is only practical as a loose coaptation of the cut ends by meticulous microsurgical techniques. The use of interfascicular suture, which is recommended to avoid misdirection in peripheral nerves,[56,57] is absolutely unfeasible and impossible in this setting. Of all factors influencing nerve recovery, the timing and technique of nerve repair are the only two factors over which the surgeon has direct influence. The slight, if any, advantage of an optimal metabolic state of the nerve cell for regeneration when a secondary repair is performed (that is, usually 3 weeks after transection) does not justify a second intracranial operation. The studies described above show that even repair of the smallest cranial nerve (trochlear nerve) is feasible; however, technical problems may arise in accomplishing accurate coaptation of the small and fragile structure. The most established surgical method for nerve

repair, one involving suture repair with fine surgical thread (8-0 to 11-0 nylon), poses several disadvantages. The sutures may be difficult to place and are easily torn from the tissue. Moreover, they may cause mechanical damage during insertion, result in a foreign body reaction, or scar and neuroma formation: all of which have negative effects on the functional outcome. Finally, a high level of surgical skill is required to perform suture repair. As regenerating axons advance by a push-pull mechanism, it is obvious that productive and blocking changes in the tissue around and between the ends of nerve sutures cause impaired regeneration. In addition, from studies on spinal nerves (which are histologically similar to cranial nerves) it appears that histiocytic cells are present in the tissue during wound healing and contribute to the thickening of the nerve sheaths after microsurgical suture repair.[54] This may impair the nutritional conditions of axons and supportive cells, because the normally thin perineurial layers of the nerves, which lack a continuous basal lamina, suggest a metabolic interrelationship between CSF and the endoneurial compartment of the nerves. Consequently, repeated attempts have been made to find a "suture-free" repair technique. Currently, different methods of coaptation have been described for cranial nerve repair such as the use of fenestrated collagen splints,[29] microfibrillar collagen tubes,[3] fibrin glues,[40] and lasers.[45]

The use of fibrin glue for nerve repair is based on the bonding properties of two substances, thrombin and fibrinogen, when they are mixed.[60,85] The results of the use of fibrin glue in experimental studies in peripheral and cranial nerves are very contrasting.[12,53,85,89] In cranial nerve repair, Sandvoss, et al.,[71,72] claim superior results with fibrin glue, whereas Seifert and Stolke[75,76] found a high dehiscence percentage and only partial recovery of the nerves coapted with fibrin glue. No specific explanation is given for these failures, but it seems to be related to the low bonding strength of fibrin glue. On the other hand, the use of a plasma clot, which is considered an inferior alternative to the commercially available fibrin glue (Tissucol), gave excellent results in rats, showing no dehiscence and good regeneration. As can be concluded from the histological figures in the paper of Fernandez, et al.,[26] the plasma clot produced a very accurate coaptation without scarring, neuroma, or inflammation. In conclusion, supported also by the clinical reports (Tables 1 and 3), there are few reasons why fibrin glue should not be used in an absolutely tension free repair of cranial nerves.

Laser welding is another alternative method for sutureless nerve repair.[55] It is a photothermal process using laser energy to join tissues, resulting in alteration of the molecular structure of the tissue being joined. The altered tissue molecules form bonds with their neighbors. The CO₂ milliwatt laser attached to the surgical microscope with a micromanipulator offers advantages such as precise spatial and temporal confinement of the applied energy that enables very localized microsurgery, which could be important, especially in areas of limited surgical access and areas involving delicate structures such as the brainstem. This was clearly demonstrated by Seifert and Stolke[75,76] who repaired the oculomotor nerve in cats and found that suture repair was not feasible because of the limited operating field. Moreover, laser repair offers the advantages that it is nontactile, induces no foreign body reaction, and the bond is definite.[55] Animal studies showed that laser-assisted nerve repair is superior to sutures in peripheral nerve repair[4,11,30] and superior to fibrin glue in cat cranial nerve repair.[75,76] Clinically, laser-assisted cranial nerve repair has been performed in a few cases by Powers using Gelfoam as a supporting membrane.[45]

End-to-End Versus Graft Repair

End-to-end repair at the time of initial surgery is now considered to be the management of choice. However, when a gap exists between the nerve ends, direct approximation carries the risk of creating

tension at the repair site (causing connective tissue proliferation and thus being detrimental to nerve regeneration), dehiscence in the postoperative period, or unnecessary stretching of the nerve (with concomitant damage to the nerve and transition zone). For the cranial nerves three and six an end-to-end repair is not possible if the gap exceeds 3 mm.[77] In these cases nerve grafting should be performed. In peripheral nerve surgery it has been proven that grafting with an autologous nerve gives the best results for histological and functional recovery.

Theoretically, it seems to us that the use of a peripheral nerve graft may be beneficial, not simply from a mechanical point of view. First, the peripheral nerve graft with its firm epineurium and perineurium can be attached to the cranial nerve stump, providing support for the sutures. Second, the connective tissue in the peripheral nerve serves as anatomical structure and guidance for growing axons, full of local factors promoting nerve regeneration.[50] In this aspect it is noteworthy that the perineurial cells in the peripheral nerve graft are the first to be involved in the cellular connection between the nerve stumps.[74] In addition, the basal lamina in the peripheral nerve is an excellent substrate for the growth of nerve fibers.[10,14,35] It provides the tracks guiding the growing axon sprouts to the target tissue. Nevertheless, these advantages must outweigh the disadvantages of grafting. In addition to harvesting the nerve graft, two graft repair sites have to be crossed by the regenerating axons. Axonal loss at each repair site may be considerable, especially in poorly performed repairs; some axons may be blocked by developing scar tissue, others may be misdirected as they advance and ultimately fail to reach and establish appropriate connections with functionally related end organs. Only Jääskeläinen, et al.,[39] question the suitability of a peripheral nerve graft. In their report, the best result was achieved in a patient in whom the statoacoustic nerve was used as a graft. Future experiments are necessary to clarify this issue.

For the reasons above described, when grafting is necessary, autologous nerve tissue should be taken. The posterior auricular nerve is recommended because of its anatomical proximity and its similar diameter. Alternatives include cervical, sural, supraorbital, or branches of the radial nerve. Nevertheless, Glasby, et al.,[32] successfully used freeze-thawed muscle autograft for cranial nerve grafting in a sheep model and in two clinical cases of facial nerve repair in the cerebellopontine angle. This muscle autograft is an oriented basement membrane matrix that does not contain Schwann cells. Therefore, it performs only over a short distance, most likely because it lacks Schwann cells. Its clinical use must be proven in the near future.

Recovery of Function

Functional recovery after nerve suturing depends primarily on reestablishment of appropriate sensory and motor connections and the preexistent function of the muscle-nerve unit. Although only a limited number of cranial nerve repairs have been performed, some considerations in the expected recovery can be postulated. Pure motor nerves are likely to regenerate better than mixed nerves where the possibility of fibers regenerating down inappropriate sheaths exists, whereas nerves innervating only one muscle have a better prognosis, eliminating functional compromise due to aberrant regeneration. Good prognosis can be expected in the fourth and sixth nerve because they are purely motor nerves, having only one muscle to innervate (Table 1). In these nerve repairs, binocular function was improved. Concerning the oculomotor nerve, only partial return of function can be expected because it is a complex nerve supplying six different muscles with specific function. The difficulty does not lie in the inadequate regenerative response, but in the apparent randomness with which regenerating axons form connections with their target organs. The axons terminate in ocular muscles other than those they originally

innervated. A classic sign of aberrant innervation consists of the mass movement of all the muscles supplied by the nerve. The reason for the failure of central reorganization of oculomotor function after regeneration remains unclear. Nevertheless, repairing the oculomotor nerve is beneficial from a cosmetic point of view. Almost all patients with oculomotor nerve repair showed useful recovery of nerve function, which prevented diplopia on horizontal gaze position (Table 1).

After facial nerve repair, patients often exhibit the phenomenon of synkinesis in the form of associated movements, mass action, or blinking tic occurring during voluntary or reflex activity. Excellent recovery cannot be achieved; once the nerve is divided, subtle facial movements are permanently lost. Nevertheless after facial nerve repair a high percentage of patients (50%) have good or fair results, regardless of the type of repair (Table 3). The major advantage of appropriate direct facial nerve repair is the restoration of facial tone at rest, degree of voluntary motion and possibility of facial motion with emotional expression.[9,39] Only in 25% of patients does poor or no recovery occur. The cause may be dehiscence of the repair site [8,52] in the postoperative period or severe preexistent facial nerve deficit.[86] Jääskeläinen, et al.,[39] found that the type of repair and the number of sutures were not associated with poor outcome. The mean time between surgery and start of the recovery is usually 6 months,[40,42] with a range of 4[3,42] to several years.[66] Although some authors state that after 2 years, further recovery of the facial nerve function cannot be expected,[3,42] it is generally accepted that maximum recovery after facial nerve repair can proceed for up to 10 years after surgery.

In cases of failure after primary facial repair, secondary reanimation techniques such as hypoglossal-facial nerve coaptation will still produce a reasonable degree of recovery.[42,52,70] In general, patients with a hypoglossal-facial nerve coaptation can achieve a House and Brackmann Grade IV or in some instances even a Grade III.[42,70] This technique gives good voluntary and occasionally some emotional movement after a long duration of practice and training. Other substitution techniques such as cross-nerve-facial nerve coaptation also achieve acceptable results, that is, a House and Brackmann Grade III in 50% of the cases.[52,70]

Limited information has been published on the recovery of other cranial nerves after repair. It seems reasonable to conclude that at least some functional recovery can occur after repair, especially in those cases with normal preoperative function. Consequently, every cranial nerve transection should be considered for repair, with the exception of the vestibulocochlear nerve. This nerve has a very long central portion[66] and must be considered as being a part of the central nervous system and thus to have poor regenerative potential.

The difference between the duration of anatomical recovery in clinical models and functional recovery in humans cannot be explained solely by the difference in the speed of regenerative response. After anatomical restoration of the nerve, peripheral deletion of maladaptive terminations and central remodeling of reflex arcs continue, which offers additional possibilities for functional recovery. Incorrect peripheral reinnervation leads to a new pattern of sensory impulses in afferent fibers and to a new cortical projection of peripheral cutaneous areas and motor representation. Thus, although the complexity of peripheral factors influencing axonal regeneration is striking, the central nervous system component of the problem is equally important. Sensory reeducation, implying a detailed program for cerebral adaptation to the new situation, represents an important component of rehabilitation following nerve injuries.

Finally, difficulties arise as to how to evaluate the recovery of the cranial nerves objectively, especially

those with complex function such as the oculomotor nerve. For the facial nerve, a uniform test has been established by the House and Brackmann grading system.[36] For other nerves, several tests have been proposed but none of them is widely accepted.[7,79] Future studies will be necessary to address this complex issue.

CONCLUSIONS

Cranial nerve injury ranks high in terms of morbidity and disability after skull base surgery. Since the first clinical report by Dott,[16] intracranial facial nerve repair is currently used by many surgeons. Subsequently, other cranial nerves have been repaired with a satisfactory degree of functional recovery. The results of these studies should encourage attempts to surgically repair cranial nerve injuries and to elicit further interest in this exciting research area.

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