

Peripheral Nerve Allograft, a Reconstructive Solution: Outcomes and Benefits

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Rezumat

Allografa de nerv periferic, o soluție reconstructivă: rezultate și utilitate

La scară planetară, în fiecare an, milioane de indivizi necesită procedee reconstructive complexe în urma a diverse traume. Recentele succese obținute în allotransplantele de țesuturi compozite, atestă faptul că allogrefele în general au un potențial spectaculos în chirurgia reconstructivă. Allografa de nerv periferic este un teritoriu de cercetare relativ recent și cu multe aspecte încă neelucidate. Principalele direcții legate de studiul allogrefei de nerv sunt reprezentate de prelevarea de la cadavru sau donator viu, denaturarea și conservarea allogrefelor, toleranța organismului receptor la allogrefă, utilizarea medicației imunosupresoare, cuantificarea rezultatelor obținute în urma regenerării nervoase.

Cuvinte cheie: nerv periferic, defect de nerv, allogrefă de nerv, prelevare de la cadavru, donator viu, rezultate clinice, limite, perspective

Abstract

Every year millions of individuals worldwide require complex reconstructive procedures as a result of various traumatic

events. Recent success in composite tissue allotransplant, has shown that allografts generally present an enormous potential in reconstructive surgery. Peripheral nerve allograft represents a relatively new research field, therefore many aspects are still to be clarified. The main interests of this study concerning nerve allograft are directed to harvesting from cadaver or living donor, allografts denaturation and conservation, recipient tolerance to allograft, immunosuppressive medication, and quantifying the outcomes of nerve regeneration.

Key words: peripheral nerve, nerve defect, nerve allograft, harvesting from donor's cadaver, living donor, clinical findings, limitations, opportunities

Introduction

Every year thousands of people worldwide suffer from post-traumatic or surgical injuries of peripheral nerves. These injuries lead to disabilities, and impaired sensory-motor nerve function. Frequently many of the untreated injuries evolve in the lack of reconstructive strategies.

Nerve allograft has been accepted since last century as a valid therapeutic choice, on the premises that the allograft allows nerve regeneration with distal reinnervation of the affected segment. Pollard et al., 1973, carried out a study on Wistar laboratory rats, covering with allograft 4 cm long defects on the sciatic nerve trajectory. Imuran (azathioprine) provided immunosuppression, and nerve regeneration through the grafts was assessed by clinically, electrophysiologically, and histologically (1). Furthermore, Cyclosporin A and FK 506 (Tacrolimus) crucially contributed to the success of composite

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tissue allografts, as main immunosuppressive medication in the protocols.

Since the ability of spontaneous regeneration of the peripheral nervous tissue is limited, the development of strategies to assist the progress of axonal regeneration is of utmost importance in the process of healing of peripheral nerve injuries. Although the autotransplant is further considered the golden standard in the reconstruction of peripheral nerve defects, the autologous material is limited and its use leads to secondary morbidity. The allografts harvested from cadavers or living donor represent an attractive choice for patients where the autograft is unfeasible or undesirable.

However, the use of allografts raises several issues: immune rejection and immunogenicity, antigenicity decrease (irradiation, freeze drying, freezing), immunosuppression (Cyclosporine and Tacrolimus).

The allograft is useful where major brachial plexus injuries are involved, as well as trauma involving nerves injuries in the extremities, conditions in which the autograft is not enough to cover the whole lesion. Therefore, the allograft harvested from cadaver (cadaveric allograft), sterilized and denatured, used as a nerve graft, represents a choice. These allografts are actually nervous bundles harvested from a variety of nerves in the body, including major ones such as the sciatic nerve. Consequently, the product provided is similar to the skin allograft used in severe burns.

Revitalisation method, clinical utility

Historically, it seems that the first nerve allograft was carried out in 1885 (2,3) when Albert (Operation an Nerven, 1885) used a 3 cm nerve allograft harvested from a cadaver, in order to reconstruct a median nerve defect, after a sarcoma removal.

1999 - nerve regeneration in human hand allograft

Dubernard et al. (4,5,6) presented in 1999 preliminary results concerning the right forearm transplant of a brain-dead patient on to a patient aged 48. Early results showed that thoracic limb allograft was technically feasible and immunosuppression prevented the acute rejection of the transplanted limb. Nerve reconstruction implied median, ulnar, and posterior interosseus branch nerves sutures. However, nerve regeneration was difficult to assess on the transplantation in progress. Observation of Tinel's sign showed consistent distal progression (from 20 cm at 100 days to at least 24 cm at 165 days). Deep pressure sensation could be felt by the patient at the mid palm after 180 days. Extreme light touch sensation was normal only at 12 cm distal to median and ulnar anastomotic sites. These clinical findings were consistent with motor and sensory nerve regeneration in human allografting.

2001 - human nerve allograft

In 2001 Mackinnon et al. (7,8) reported seven patients who underwent reconstruction of long peripheral nerve gaps with interposition of the allografts, both in upper and lower limbs. The patients were selected among those showing

nerve gaps exceeding the length that could be reconstructed with available autograft nervous tissue. Before transplantation, the cadaveric allografts were harvested and preserved at 5° C. In the interim, patients received an immunosuppressive regimen consisting of Tacrolimus, Azathioprine, and Prednisone. The immunosuppression was discontinued 6 months after the nervous regeneration across the allograft was obvious. Six patients showed the motor and sensory function recovery in the affected limb, and one patient experienced the allograft rejection secondary to subtherapeutic immunosuppression.

In addition to providing the ability to restore nerve continuity in severe extremity injuries, successful nerve allografting protocols had direct applicability to composite tissue transplantation.

Furthermore, peripheral nerve allografts were performed in patients aged 3-24 years (9). The surgical indication for the graft was a large deficit secondary to trauma, that could not be reconstructed conventionally. Nerve allografting was carried out in the upper limb (four patients), and in the lower limb (three patients); two patients received allografts only, and five patients received both allografts and autografts.

The above are the findings of Mackinnon and collaborators who performed nerve allografts on seven patients from 1992 to 2001 (7,8).

2006 - brachial plexus

In 2006, Elkwood et al. (10) reported, seven cases of brachial plexus injuries selected for grafting using either living-related donors or cadaveric allografts (in one patient). Immunosuppression was tolerated with no complications. There were no graft rejections and six patients showed functional recovery.

Therefore the nerve allograft allowed long peripheral nerve defects reconstruction. In patients with multiple and superimposed brachial plexus injuries, the allograft granted a more complete reconstruction, leading to functional recovery to a greater extent. (2)

2006 - specific features of nerve regeneration after face and hand allotransplantation

Recovery after human hand transplant was similar to nerve regeneration after an injury with peripheral nerve section. In 6-12 months all patients recovered the protective sensibility, 88% reaching to discriminatory sensitivity (11). Overall, the functional outcome and patient satisfaction were reported as good.

The recovery of motor function enabled the patients to perform most daily activities (eating, driving, objects grasping, using a bicycle or motorcycle, shaving, using the phone, writing). In 2 years all patients returned to work managing to cope with previous activities and in some cases improving their ability to work, and filling higher positions. Therefore the quality of life improved in 83% of cases (11).

However, the most important issues regarding face transplantation were related to the vascular survival of the facial flap and nerve regeneration through the transplanted face.

A successful face transplantation implied the transplant to show a normal final appearance with the possibility of mimicry (12,13). This depended on normal healing of muscle sutures, and on nerve regeneration along the facial nerve. Hand and peripheral nerves allografts showed a faster nerve regeneration as compared to the autograft due to the FK506 influence on axonal regeneration. Therefore, the recovery of sensitivity and mimic after transplantation was considered to be one of the most important markers of face transplantation.

2007 - complications after human allograft

Although nerve allografts of different origin and unlimited potential, represented a solution for peripheral nerve regeneration, studies had shown that nerve regeneration required immunosuppression until reaching connections with the target organ. Therefore immunotherapy was interrupted in order to prevent undesirable side effects.

Clinical severe damage, increased nerve regeneration potential, as the availability of prevailing allografts from living donors represented an attractive solution for the reconstruction of peripheral nerves in pediatric patients.

Larsen et al. (14) reported in 2007 a case (child aged 1 year with obstetric brachial plexus paralysis) who had received an allograft from a living donor, that was positive for Epstein – Barr virus. Consequently, the child quickly developed a symptomatic form of disease concurrent with immunosuppression. On interrupting the premature immunosuppressive therapy, the patient experienced a short episode of illness, but the Epstein-Barr virus infection could become major life-threatening (potential severe lymphoproliferative condition). As the risk of developing a lymphoproliferative disease was lifelong, monitoring had to be considered. Therefore, the risks associated with this type of procedure were highlighted.

2009 - nerve regeneration in human upper limb allograft

Nerve regeneration concerning upper limb transplantation in humans was obvious due to sensitivity and functional restoration in the transplanted limb. Nevertheless, motor and sensitivity recovery period depended on the amputation degree (15). Sensitivity was recovered in 6-8 months and the motor function in 1 year, according to the amputation degree. However nerve regeneration was slow and progressive. Sensitivity was 98% recovered, and motility was regenerated at a rate of 90-95%.

Discussion

The recent clinical cases of hand and composite tissue allotransplantation opened a new era in the practice of reconstructive surgery. Some have suggested that hand and face(allo)transplantation could be the next step to benefit patients whose conditions can not be addressed by conventional techniques of reconstructive surgery using autologous tissues. Romanian school of surgery is at the forefront of organ autotransplants related events, the latest articles on the subject indicating the vanguard of Romanian

surgery (16,17,18,19).

Conventional microsurgery is no longer available for large nerve defects, or for those showing unique features. Typically these patients are invited to call a prosthetic center, whether the deficit involves the limbs.

Nevertheless, the patients with severe disabilities can take into account the prosthetic solutions, however these proved to be completely unsatisfactory so far. Another category of patients who require innovative solutions is represented by those with defects of face, larynx, abdominal wall, uterus, and without a prosthetic solution. Therefore, the only alternative for microsurgeons is to explore new functional free flaps harvested from cadaver donors, a concept widely accepted where internal organs are involved (organ donor).

Currently, 98 different composite tissue transplants have been carried out worldwide (hand, face, larynx, femoral shaft, knee, abdominal wall, uterus) in the near future the surgical expansion in this field is inevitable, due to safer drugs availability as well. Meanwhile, surgeons have to find the most favorable treatment option for these patients.

Allografts provide a temporary structure allowing nerve regeneration in the host and repairing major defects in the peripheral nerves. Allografts combined with immunosuppression are able to ensure nerve regeneration and functional restoration similar to autografts, as shown in studies on rodents, large animals and primates, and consistent with findings in clinical achievements. Nerve allograft requires only a temporary immunosuppression in contrast to composite tissue transplantation (20). On the other hand, peripheral nerves allografts rejection is difficult to be watched in the initial stages of nerve regeneration, as the nerves are located in deep tissues, so highlighting the functional restoration is therefore delayed.

The main advantages of nerve allograft consist in:

1. Supporting the axonal regeneration over long defects similar to autografts.
2. Already available in a potential tissue bank or to be harvested from donor and / or cadaver.
3. Easy usage, with good results, combined with immunosuppression.

Therefore allografts immunogenicity rejection can be achieved by denaturing (chemical, thermal). It would be of interest to experimentally watch the opportunity of replacing the need for immunosuppression, by means of dynamic interference in denaturing. Furthermore, allografts freezing decreases the antigenicity, in direct proportion to the necessary time required by maintaining a low temperature (21).

Conclusion

Nerve allograft represents an exciting therapeutic choice, even without validation due to long-term experimental studies. Nerve regeneration through allografts in immunosuppressed recipients is equivalent to autograft.

Allograft harvesting from cadavers, within the limits of well-defined rules (preservation, denaturing, limited immunosuppression) can represent a real gold mine regarding

peripheral nerves reconstruction in the near future.

Immunosuppression can be successfully interrupted after reaching the target organ reinnervation. Although the clinical results are very promising, the clinical therapeutic decision on peripheral nerve allograft transplantation remains far from any standardization.

Due to the lack of more advanced choices, the nerve allograft is allowed for clinical use only under special circumstances, until further conclusive positive results are available, and taking into account the principle of *primum non nocere*.

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