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Recent advances on acute paraplegia

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ABSTRACT

Paraplegia and spinal cord injuries are issues of major concern to the actual medicine. But recent advances have raised hopes for a better prognosis, which has always been poor or infaust since medicine was practiced. However and interestingly enough, some concepts and definitions on the occurrence have survived for millennia. Once encountered as an issue, traumatic or non-traumatic paraplegia needs a multidisciplinary approach and a careful staging of the problem. Different scales are available with Frankel's and American Spinal Injury Association most widely used as alternatives or complementary tools. The authors discuss therapeutic options with a special focus on the stem cell therapy which has seen an impressive increase on the number of trials for a successful treatment. Sourcing and yielding of stem cells are made possible through a number of techniques, with material aspirated from bone marrow or adipose tissue, which are used along with other sources of neuronal precursors such as olfactory ensheathing cells. Nevertheless, large and multicenter studies are still lacking. However, with the quality of the ongoing work and research, the optimistic attitude seems warranted. Meanwhile, other rehabilitation and medical care interventions, always at hand, need to be applied in every individual suffering from paraplegia and spinal cord injury.

1. Introduction

The traumatic, and even more the non-traumatic paraplegia, always remaining a diagnostic and clinical challenge, has been a part of medical discussions and publications ever since quotations become an unavoidable element of the academic writings. In his prolific and pioneering work, Graves dedicated an entire lecture to the issue of paralysis, though he explicitly chose the term 'paraplegia' as its running head[1]. At that remote time of the 19th century, finding out that nervous injuries could follow a centripetal trajectory was highly sensitive, as Graves wrote: "When a certain portion of the extreme branches of the nervous tree has suffered an injury, the lesion is not confined merely to the part injured, but in many instances is propagated back towards the nervous centers"[1]. After marshaling several arguments that mirrored the general medical opinion of that time, paraplegia occurred due to bowel inflammation or enteritis. Nevertheless, Graves accepted that arsenical or lead poisoning might quite well be an etiological factor, with both the irritants acting directly on the central nervous system[1].

The paralysis of the lower extremities was more descriptive and detailed in the second volume of Leroy d' Étiolles work published in 1857, which was widely deemed as a reference source from his contemporaries[2]. After dedicating an entire chapter to empoisonings leading to paraplegia (with a particular emphasis on arsenical paralysis), and without avoiding the notion of 'intestinal irritation' with a copious list of causative infections in the sixth chapter of his work, the French physician spoke about an idiopathic paraplegia in the ensuing chapter of his work.

A single search on the PubMed with the term 'paraplegia' will produce more than 19 700 quotations, with the most distant one dating in 1827[3]. Earle took care of initial definition of the term in his collection of cases, and for that precise reason, he summoned several previous designations: "Hippocrates denominates all paralytic affections occurring after apoplexy,

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paraplegia. Aretaeus uses the word to denote a remission of sensation or motion in some one particular part. Boerhaave says that paraplegia is a palsy of all parts below the neck"[3].

The long list of the alleged etiological factors of non-traumatic paraplegia of an unknown origin was confusing to historical authors of the medicine of 19th century. Brown-Séquard numbered more than twelve conditions leading to this event in a part of one of his lectures. He wrote about 'cases of paraplegia' due to diseases of the uterus, the urethra, the bladder and prostate, nephritis and enteritis, as well as due to affections of lungs or pleura, diphtheria, diseases of the knee joints, irritation of the nerves of the skin and neuralgia, and even due to teething. It seems that the famous physician had his own doubts on the veracity of the factors included in the list. Therefore, he intuitively recollected all of those under the term of 'reflex paraplegia'. His work, originally published as a lecture in The Lancet in 1860, was thereafter printed in its complete form Williams and Norgate[4].

After such a disparate historical spectrum of alleged factors leading to non-traumatic paraplegia, it is obvious that the proposed medical treatments of the period actually are of a pure curiosity and largely obsolete. Graves mentioned several experiences of his own treatment through purgatives, cupping to the nape of the neck, diluents and opiates, moxae (a plant-parasitic nematode) applied along the course of the spinal column, blisters and liniments over the calf and the trajectory of the sciatica. But he concluded that 'strychnine' and 'sulphur' are the only internal remedies of benefit[1].

2. Classificatory attempts

Clear as it is, the term paraplegia is equivalent to a complete paralysis of the legs and the lower body. Incomplete lesions are given the denotation of paraparesis. Hippocrates was the first one to introduce the term, and his definition was given at the introductory notes. The famous physician thought that the occurrence was related with a blow of the disease, whence 'stroke'[5]. The word itself is composed from para (παρα – beside, from the Greek) and plessēin (πληγή – to strike, from the Greek).

The word itself has an ominous hint. In fact, the morbidity and disability produced from complete spinal cord lesions are exceptionally high. However, in view of continuous medical research and progress, infaust prognosis might not always be inescapable. The change of the prestigious journal titled 'Paraplegia' (published in 1963–1996) into 'Spinal cord' (since 1996 one of the journals of Springer Nature) reflects fairly well the optimistic attitude that is characterized over the last two decades.

In order to assess the severity of the neurological impairment, several scales have been proposed. Frankel scale, proposed in 1969, was a simple measure of 5-points (Table 1).

The American Spinal Injury Association (ASIA) and the International Spinal Cord Society have proposed another scale, modifying the Frankel's, and this is actually the most widely used clinical tool to quantify the severity of SCI[7]. The revised scale, known as the 'ASIA Impairment Scale', is reproduced in Table 2. Meanwhile, the international standards for the neurological classification of the SCI are reviewed and revised several times[8,9].

Other authors have suggested that relying on the sacral sparing as a criterion for complete spinal injury is more reliable than the criteria used by ASIA, which depends on the neurological level of injury and the width of the zone of partial preservation[10]. Obviously, sacral sparing of some functionality is of particular significance in view of preservation of some involuntary sphincter contractility. However, these slight classificatory changes in between sources are not conceptual, and the impairment scales correspond largely to one another. Most importantly, grading the severity of the spinal cord trauma has a clear prognostic value, since a complete injury after the initial acute phase has a poor outcome; it seems that the first 24 h is not only decisive, but sufficient to draw conclusions about the completeness or not of the irreversibility of the spinal injury[11].

3. Treatment: from bench to bedside

Large-scale studies have been so far mainly focused on the timeliness and dosage of methylprednisolone, whose efficacy during the acute phase of SCI is widely accepted. Three studies named National Acute Spinal Cord Injury I, II and III have already published their promising results[12–14]. High-dose dexamethasone is another glucocorticoid agent applied with some efficacy[15]. Among the disparate pharmacological options suggested and applied by different authors with some extent of efficacy, other potent glucocorticoids have been suggested (such as tirilazad mesylate), even through combining steroid therapy with local hypothermia. But GM1 ganglioside, naloxone, 4-aminopyridine, guanosine derivatives and agents with stem/progenitor cell proliferative properties (such as curcumin) have been tried as well[12–19]. Electrostimulation (alternating current stimulation) and elective neurosurgery (decompressive laminectomy) should be taken into consideration accordingly. Nevertheless, the actual focus of study has been shifted toward transplantation modalities, namely, the stem cell therapy.

Albeit not unknown to the scientific circles, stem cell therapy for SCI is a relatively new method. However, its successful application in a diversity of studies, some of which have already achieved their second phase, has raised consistent hopes[17–19]. The first issue of concern is where to find and produce enough precursors of the neurons, largely damaged during the SCI.

Table 1
The Frankel scale for spinal cord injury (SCI)[6].

Frankel scale		Characteristics
A	Complete	No motor or sensory function below level of lesion
B	Sensory only	No motor function, but some sensation is preserved below level of lesion
C	Motor useless	Some motor function without practical application
D	Motor useful	Useful motor function below level of lesion
E	Recovery	Normal motor and sensory function, may have reflex abnormalities

Table 2
ASIA impairment scale[7].

ASIA impairment scale		Lesion
A	No sensory or motor function is preserved in the sacral segments S4–S5	Complete
B	Sensory but no motor function is preserved below the neurological level, including the sacral segments S4–S5	Incomplete
C	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3	Incomplete
D	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more	Incomplete
E	Motor and sensory functions are normal	Normal

The second issue is the way of administration (local *vs.* systemic), although most scholars do inject those intrathecally, why not directly over the spinal level of lesion especially when it has a traumatic nature. But other dilemmas remain as well, such as those related to the frequency of administration, the dosage of stem cells to be injected, and last but not least, the final outcome or the overall success of a sophisticated technique[20]. On the other hand, some studies reporting successful treatment and optimistic outcomes have been performed on rats, hence the efficacy on humans cannot be taken for granted[20–22].

Before considering alternative sources of stem cells, direct transplantations of human neurons have been tried, mainly through the usage of clonal forms such as human neuroteratocarcinoma neurons derived from the human neuroteratocarcinoma[21]. Bone marrow stromal cells have been successfully transplanted in traumatic central spinal cord cavities of adult rats with chronic paraplegia[22].

Back to humans, the results of an open-label study conducted on 297 patients regarding the efficacy of autologous human bone marrow derived mononuclear cell transplantation in SCI have been reported[23]. It seems that over the last decade, the research has been focused on the following sources of stem cells: a. autologous human bone marrow derived mononuclear cells, with the bone marrow aspirated from the anterior iliac crest and isolation of the mononuclear fraction by density gradient method[17,19]; b. co-infusion of autologous adipose tissue derived mesenchymal stem cell differentiated neuronal cells and hematopoietic stem cells[18]. For this purpose, adipose tissue was resected from patients' anterior abdominal wall.

ASIA score has been the standard methodology for reporting results and outcome of the studies. Some authors have also reported those results strictly related with the ambulation ability of the patients through the Hauser index[18,24]. Hauser ambulation index will obviously ponder the ability/disability and the severity of the latter with regard to motor activity of the lower extremities, without evaluating any left sensorial capacity. However, the ambulation index through focusing on the remaining motor activities, if any, will reflect fairly well the functionality of the spinal cord below the level of the injury, although the index itself was not originally conceived for SCI evaluation (Table 3).

Table 3
Hauser ambulation index[24].

Index	Characteristics
0	Asymptomatic; fully active
1	Walks normally, but reports fatigue that interferes with athletic or other demanding activities
2	Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 m) in 10 s or less
3	Walks independently; able to walk 25 feet in 20 s or less
4	Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 s or less
5	Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 s or less; or requires unilateral support but needs more than 20 s to walk 25 feet
6	Requires bilateral support and more than 20 s to walk 25 feet; may use wheelchair on occasion
7	Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair for most activities
8	Restricted to wheelchair; able to transfer self independently
9	Restricted to wheelchair; unable to transfer self independently

Of course, sensation repair in SCI patients under therapy must be also tested, evaluated and methodologically scored as well as other vital functions that are not related to ambulation, but extremely important, such as the bladder control[25].

The actual trend of stem cell sourcing purposefully used to treat SCI and paraplegia among human patients seems to confirm that these techniques might yield better and more reproducible results. However, the use of genuine neural precursors, such as human neuroteratocarcinoma or olfactory ensheathing cells, previously tried in pioneering studies in rats and actually even in humans, is of interest[26,27].

The predilection of different methodologies in producing stem cells might be related with technical issues, such as the ease of obtaining bone marrow material aspirated from the iliac crest or adipose tissue from the abdominal wall (generating neuronal stem cells from autologous tissue derived mesenchymal precursors). But a diversity of factors will influence the overall success of a transplantation attempt.

4. Conclusive remarks

With the wide acceptance of efficacy of glucocorticoids during the acute phase of SCI, and following grounded and numerous reports of stem cell transplantation success in the chronic phase of

paraplegia, it seems that actually the treatment guidelines, if not yet clear-cut are extensively outlined. Optimistic approaches toward stem cell therapy have even pushed scholars to advise repeated transplantation efforts[25]. The timeliness of such transplantations has been discussed as well. In general, efforts should be started one year following the initial injury, when the expectances for a natural recovery become almost zero.

Meanwhile, other aspects of treatment and support of paraplegia patients need to be considered and taken care of. Being severely handicapped will not necessarily mean a complete loss of the sense of life. Surprisingly enough, in what is called the "disability paradox", persons with severe impairments tend to have high quality of life[28]. Such a potential must be fully exploited, even for psychotherapeutic means.

In a thorough review, Mukand *et al.*[29] considered the organ and systemic long-term complications of SCI. Table 4 summarizes those findings and caveats.

Table 4
Systemic SCI complications[29].

Position	Complications
Pulmonary	Breathing and coughing impairment; atelectasis and aspiration pneumonia; impaired clearing of secretions; complications of prolonged intubation (tracheal stenosis)
Cardiovascular	Thromboembolism; deep venous thrombosis; neurogenic orthostatic hypotension; silent myocardial ischemia; autonomic dysreflexia
Genitourinary	Renal failure; urinary incontinence predisposing to decubitus ulcers; complications of indwelling catheters (calculi, fistulas); bladder dysfunction
Gastrointestinal	Constipation; ileus; fecal impaction; gastric ulcer; gastro-esophageal reflux; nausea; incontinence
Integumentary	Decubitus ulcers
Metabolic	Heterotopic ossification

The list of SCI complications cannot be exhaustive. However, it is clear that a prompt detection of the occurrences described in Table 4 will be helpful for an adequate and effective treatment of those.

Rehabilitation procedures should be put in place as soon as the general status of the patient allows that, and individually planned and implemented. Pain is a frequent and sometimes neglected problem, especially in its neuropathic form. Recently, some guidelines have been approved in order to standardize its handling[30]. Orthopedic interventions, even corrective or palliative, must be considered. Different kinds of jackets, orthosis, splints, casts and immobilization devices are available, apart from surgical options[31,32]. With the high frequency of SCIs following traumatic events, it is not even surprising that some authors are testing protective devices *ad hoc* for protecting the nervous structures[33]. Once considered as a curse, the prognosis of SCI and paraplegia is expected to change substantially, with more research focused on stem cell transplantation options, and with the up-to-date optimistic reports from different sources treating this medical condition.

Conflict of interest statement

The authors report no conflict of interest.

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