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Re-Engineering of the Damaged Brain and Spinal Cord

Evidence-Based Neurorehabilitation

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Edited by
K. R. H von Wild
In Cooperation with G. A. Brunelli

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Preface

Re-Engineering of the Damaged Brain and Spinal Cord
is dedicated to Tetsuo Kanno, M.D.
Professor of Neurosurgery

By presenting the original papers that make up this third supplement we wish to make a further contribution to the issue of functional rehabilitation, this so important and fascinating modern area of research in the field of neurosciences. The congress papers we have selected constitute a good reflection of the transdisciplinary objectives. The literature references are designed as a guide to lead the interested reader to a deeper and more detailed understanding of the individual issues.

Functional rehabilitation has been an original task of neurosurgery from the very outset. The 1990s have entered the annals of brain research as the ''Decade of the Brain''. Since then there has been an ever stronger growth of neuroscientific interest worldwide, accompanied by substantial financial engagement. This has primarily resulted in advances in basic neurobiological and neurophysiological research and also in the growth of neuroscientific knowledge about basic mechanisms for motor control, pain control, awareness, cognition, learning and memory. The consequence must be to ensure that the advances made in the neuroscientific research area are adequately expanded into practical neurosurgical care and re-engineering of brain and spinal cord lesions and to ensure upon new approaches. Following this a fundamental path will result in an improved and more efficient prevention in the future, the measures that stand right at the forefront of all rehabilitation principles, meaning that conventional concepts must be modified to keep pace with the more task-specific, intensive, and progressive demands. In this connection a series of guidelines, recommendations, and expert opinions and also algorithms have been elaborated by national and international expert panels and multidisciplinary associations for the acute medical care of patients. Experience has shown that these guidelines and recommendations must not be infrequently modified to the features of the local medical landscape in the regions where they are enacted. What is more, progressive new findings must be also subjected to a frequent revision. On top of this, it should not be forgotten that even when committal therapy guidelines are consistently applied, there are considerable variations in the range of potential complications and in the outcome of prospective controlled multi-centre and multinational studies on the issue of quality management.

The demand for ''evidence-based medicine'' is well justified; however, it rapidly comes up against the limits of feasibility, especially where controlled therapeutic studies are concerned. The Cochran collection of high-quality evidence-based healthcare databases has thus far been of no help to us in drawing up therapeutic recommendations for the re-engineering of brain and spinal-cord lesions. Today as ever, the opinion of experts and empirically based medical treatment and posttraumatic neurorehabilitation continue to occupy an indispensable position for the everyday clinical practice of neurosurgical and neurotraumatological therapies. Promising adjunct approaches include neuropharmacology, for cascades of molecular interactions are known to be underlying activity-dependent plasticity and skills learning, as many of these processes involve the major transmitters. Furthermore, biological interventions by using endogenous neurons and glia as well as exogenous stem cells, bone-marrow cells, macrophages, and other types may promote the regeneration of nerve cells, tissue, and neural circuitry. Class one studies have been made, and now class two studies have been initiated, for example in connection with acute spinal cord injury (SCI). The clinical application of functional electrical stimulation (FES), the use of Neuroprosthesis, recently brain-mind interface technology, and robotic devices are still at the experimental stage;

however, in the near future these may become helpful adjuncts in restoring impaired and even lost motor and sensory functions in connection with brain and spinal cord lesions. Clinicians working in the fields of post-traumatic rehabilitation and re-engineering may now design and test novel therapies that have shown their potential value in animal experiments and preliminary human studies in manipulating the central nervous system to less impairment, disabilities, and functional limitations. Brunelli's paradigm of the CNS-PNS connection in SCI is one such characteristic example of the novel opportunities for neural repair. This opens up an entirely new challenge for all neurosurgeons and neurotraumatologists interested in multidisciplinary cooperation working at developing new strategies for the re-engineering of brain and spinal-cord lesions.

In this connection, studies into the assurance of the quality of our medical action in acute care and holistic rehabilitation are an urgent necessity. What will be the functional outcome of the patient? Which treatment strategy promises the most favourable health-related quality of life (HRQOL) for the patient? It is precisely issues such as these that place us before a major task, one that we can successfully approach only in cooperation, in a common team consisting of neuropsychologists, neurologists, neurosurgeons, neuropaediatric specialists, gerontologists, traumatologists, orthopaedic experts, epidemiologists, and social-medicine specialists. After five years of preparation, an assessment of HRQOL in persons after TBI has now matured for clinical application. A prospective study into the quality management of acute TBI in Germany, with a response rate of 64% after just one year, for the first time ever, gives a reliable indication of the outcome after standardized acute treatment. The definition of specific measures for outcome assessment following tumour surgery, functional neurosurgery, and neurosurgical re-engineering of brain and spinal-cord lesions is one of the challenges facing the delegates of the Committee for Neurorehabilitation and indeed all neurosurgeons and rehabilitation scientists.

This volume is the third in the series of proceedings covering the official biennial conferences of the Neurorehabilitation Committee of the WFNS in connection with two other international scientific congresses on aspects of basic research and clinical issues in neurotraumatology, namely the 5th Symposium on Experimental Spinal Cord Repair and the 1st Conference of the Academy for Multidisciplinary Neurotraumatology (AMN) in Brescia in March 2004. The first volume (Volume 79/2001) on functional rehabilitation in neurosurgery and neurotraumatology highlighted the important role played by neurosurgeons in neurorehabilitation beginning at an early period after the occurrence of the brain and spinal cord lesion and the important role of neuropsychology, as it was presented at the first meeting of the WFNS Committee in Münster, Germany 2000 under my auspices, as well as selected papers from another two meetings, the 5th Annual Meeting of the Euroacademy for Multidisciplinary Neurotraumatology in Paris, September 2000, and the Workshop on Early Neuropsychological Rehabilitation, Maribor, March 2001. The second supplement (Volume 87, 2003), edited by Professor Yoichi Katayama, contains the most important manuscripts that were presented at the second conference of our WFNS committee in Tokyo in 2002, which was organized and chaired by him. The central topic of this conference was the re-engineering of brain and spinal-cord lesions. Accordingly, it presents a wide variety of neurosurgical techniques, indications, and functional results that are described in detail. The conference was run as a joint meeting with the Japan Coma Society and gave the attending experts the opportunity to visit the nearby Chiba Ryogo Centre, which is one of the best equipped institutes specializing in the neurorehabilitation of the severest cases of TBI (vegetative state) in Japan.

In continuing our endeavours to promote close multidisciplinary cooperation in functional neurosurgery, neurotraumatology, and functional neurosurgical rehabilitation and the re-engineering of brain and spinal-cord lesions, it can indeed be called a stroke of luck that Giorgio A. Brunelli, Emeritus Professor at the Orthopaedics Medical Faculty of Brescia, Italy, organized the 5th Symposium on Experimental Spinal Cord Repair in Brescia, with a joint chair in conjunction with the third conference of our WFNS committee from March 27–29, 2004. Guest of Honour of the 5th Symposium was Professa Rita LEVI-MONTALCINI, Rome, Nobel Prize Laureate in Medicine 1986, who once again inspired the audience with her unique expertise, brilliant new ideas and her critical remarks and future visions regarding both experimental and clinical spinal cord repair (Fig. 1).

Professor Brunelli, in his capacity as Vice-President and Congress President of the World Academy for Multidisciplinary Neurotraumatology (AMN), founded in 2003, he also invited the 17 founding members and guest speakers for March 29

Fig. 1. Guest of Honour, Professa Rita LEVI-MONTALCINI, Rome, Nobel Prize Laureate in Medicine 1986, for her discoveries of growth factors, sitting between Professor Giorgio A. Brunelli, Brescia, Congress President (right side) and Professor Klaus R. H. von Wild, Münster on occasion of the of the 5th Symposium on experimental spinal cord repair, Brescia, Italy, in conjunction with the 3rd Conference of the WFNS Committee on Neurorehabilitation, March 28th, 2004

and 30, so that all congress participants had ample opportunity to exchange information and experience and to hold informal discussions. It was thus an obvious option to publish the most important papers presented at these three jointly held scientific conferences covering many aspects of the re-engineering of brain and spinal-cord lesions in a third supplement and thus to make them accessible for a larger circle of interested scientists. The 42 scientific papers that have been included in this supplement reflect the current status of neuroscientific research and the clinical knowledge in this field.

First and foremost I wish to express my sincere and cordial thanks to my friend and colleague, Giorgio A. Brunelli, for his hospitality and cooperation. Not only did he manage to organize a wonderful congress with a stimulating scientific programme in Brescia, but thanks to his considerable personal experience, his recognition as an expert the world over and his many personal contacts, he was also able to create yet again just in the right atmosphere, an extraordinarily intensive scientific exchange of opinions and ideas, giving me welcome support in my endeavours.

I should also like to thank all the authors and co-authors for sending me their original papers for inclusion into this third supplement in good time, the time pressure that was placed upon them notwithstanding.

Without the careful review and the first correction of the manuscripts by Dr. Matej Lipovšek, Maribor, Slovenia, the secretary of the WFNS Committee of many years' standing, I would never have succeeded in publishing this volume. My most special thanks for this renewed demonstration of our friendship.

I also wish to say a special thank-you to Professor Dr. Hans-Jakob Steiger, the editor of Acta Neurochirurgica Supplements, for his support in the realization of this project and his attentive and constructive handling of the individual papers. My thanks also go to Mrs. S. Schilgerius from the Springer Verlag in Vienna, who yet again applied her renowned diligence and expert eye to enable the proceedings to be published in such a short time and especially in the quality that is the hallmark of her work.

Acknowledgments

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Klaus R. H. von Wild
Münster, Germany

Forewords

The subject of neurorehabilitation and the enhancement of recovery from brain and spinal cord injury is of great importance to people in every part of the world and to neurosurgeons and allied physicians who care for injured patients. Based on the remarkable advances that are occurring in molecular biology and basic neuroscience, there is every reason to believe that great strides can be made in helping patients recover from injury to the central nervous system. It is clear that these efforts will be multidisciplinary in nature, and a review such as this one emphasizes that important aspect of our endeavors.

Hopefully this is only a beginning of a new era in rehabilitation and we must admire the wisdom and the energy of all of the contributors to this outstanding effort.

Edward R. Laws
President of the WFNS
Charlottesville, Virginia, USA

The question of paraplegic and quadriplegic patients is one of the main challenges of the next decade. In Europe, there are around 300.000 paralyzed people. In France, every year, 1000 new cases are coming in addition to the 6500 patients waiting for a miracle therapy. In the clinical context of poor spontaneous regeneration in spinal cord, the difficulties to transfer in human beings the promising results obtained in animals are huge and the path to repair human injured spinal cord may be unfortunately long. However, in acute stage, there is a study going on with autologous activated macrophages whose primary results in phase I gave, for the first time, a hope for stimulating repair processes in paralyzed people. We wish that the phase II study will confirm the exciting results of phase I and that other studies will arrive for those chronic patients who are waiting with great hope from all the researches which are going on animals.

Jacques Brotchi
President-Elect and
Coordinator Scientific Committees WFNS
Professor & Chairman
Department of Neurosurgery
Erasme Academic Hospital
Brussels, Belgium

I am delighted to be holding and scrutinizing this book, the third volume in a new series of proceedings, which covers the official scientific meetings of the Neurorehabilitation Committee of the World Federation of Neurosurgical Societies (WFNS). Recent advances in functional neurosurgery have opened up an important new area in which neurosurgeons can collaborate with specialists in the multi-disciplinary aspects of neurorehabilitation, involving a wide range of neurosurgical techniques. These procedures provide benefits for the control of a wide variety of disabilities. It was for these reasons that the Neurorehabilitation Committee was founded within the WFNS.

The first scientific meeting of the WFNS Neurorehabilitation Committee was held in Munster, Germany, in 2000 under the auspices of Professor Klaus R. H. von Wild. The second scientific meeting of the WFNS Neurorehabilitation Committee was held in Tokyo, Japan, in 2002 and it was hosted by me. The second meeting placed emphasis on identifying and defining the role of neurosurgeons within the broad multi-disciplinary spectrum of neurorehabilitation. The tasks carried out through collaboration between neurosurgeons and specialists in neurorehabilitation cannot be viewed simply as a restoration of function or reconstruction of structure, since they involve extensive functional and structural reorganization of neural networks within the brain and spinal cord. On this basis, we ascribed such activities as re-engineering of the damaged brain and spinal cord, and designated the second scientific meeting as the International Symposium on Neurosurgical Re-Engineering of the Damaged Brain and Spinal Cord.

It was clear to us from these two initial meetings that this field of endeavor had undergone rapid development in close cooperation and association with relevant areas of the basic neurosciences. The third scientific meeting, on which this volume is based, was held in Brescia, Italy, on March 28–30, 2004. In order to facilitate communication and cooperation among neurosurgeons, specialists in neurorehabilitation and basic neuroscientists, the meeting was held as a joint meeting with the Academy of Multidisciplinary Neurotraumatology (AMN) just after the 5th International Symposium on Experimental Spinal Cord Repair, and the participation of a wide range of basic neuroscientists was thus encouraged. As expected, this third scientific meeting provided an excellent opportunity to share skills and knowledge among neurosurgeons and specialists in neurorehabilitation, as well as basic neuroscientists. The meeting also aroused attention and interest among neurosurgeons regarding recent progress in the basic neurosciences, and helped basic neuroscientists to discuss their achievements in the context of a clearer understanding of neurosurgical techniques. As a result, the third scientific meeting was a great success.

I congratulate Professor Giorgio A. Brunelli, the Congress President and Vice-President of AMN, and Professor George P. Prigatano, the President of AMN, for organizing the joint meeting of AMN and WFNS so successfully. I extend my thanks to Professor Klaus R. H. von Wild, the Honorary Chair and Founder of the WFNS Neurorehabilitation Committee, for his energetic efforts to arrange the third scientific meeting in Brescia. I would like to express my gratitude to them for providing us all with an excellent opportunity to interact with other specialists and investigators in different fields. I also gratefully acknowledge support from Professor Edward R. Laws, the President of the WFNS, for his unfailing assistance so generously given to the Neurorehabilitation Committee.

Yoichi Katayama
Chair of the Neurorehabilitation Committee of the
World Federation of Neurosurgical Societies

On behalf of the Academy of Multidisciplinary Neurotrauamtology (AMN), we are most pleased to have *Acta Neurochirurgica* publish as a Supplement the scientific proceedings of the first meeting of the AMN in Brescia, Italy.

It is readily apparent that the papers present a broad coverage of topics important to the neurotraumatologist. It is the expressed purpose of the AMN to foster such multidisciplinary discussion and dissemination of information between disciplines.

Patients with neurotrauma require specialist care at all levels. When specialists communicate with one another about their work and ideas, the probability of patients receiving various specialists' care increases. Such dialogue also provides the hope that multiple disciplines will collaborate in their research activities to answer clinically meaningful questions. This research obviously must be done in a scientifically robust fashion.

We are most gratified with the response to the AMN and invite our colleagues to consider joining this active, international group of individuals. Presently, the AMN represents physicians and surgeons in many disciplines, as well as a variety of healthcare providers. Our hope is that the organization will continue to foster this type of diverse membership. Our yearly meetings will attempt to focus on specific topics relevant to the neurotraumatologist. We are hopeful that those meetings will produce new insights and reinforce the enthusiasm necessary in caring for patients who have trauma to the central nervous system. For those interested in learning more about our organization, please go to our web site, www.worldamn.org.

George P. Prigatano, Ph.D.
President of the AMN
Phoenix, Arizona, USA

The International Symposium on Experimental Spinal Cord Repair and Regeneration is held every two years in Brescia on behalf of the foundation for research on spinal cord lesions.

All the branches of Medicine in any way connected to spinal cord lesions represented, with special attention to research: Basic Science, Neurology, Molecular Biology, Biochemistry, Bio-Technologies, Immunology, Experimental Surgery, Clinical Surgery, Urology, Reconstructive Surgery and rehabilitation.

Scientists from all over the world have presented their research and results obtained in the last years.

This year the 5th International symposium on experimental spinal cord repair and regeneration, thank to the active and enthusiastic cooperation of Prof. Klaus von Wild, took place together with the 1st AMN World Congress. The founder members of the Academy for Multidisciplinary Neurotraumatology presented their results in research and treatment of trauma of the central nervous system (brain and spinal cord).

The 3rd Conference of the WFNS Committee took place at the same time, as there is a combination of different scientific activities that are more or less of special interest for the same group of participants regarding neurotrauma and functional neurohabilitation with reconstructive neurosurgery.

The combination of the 3 events was certainly a great occasion to share the ideas of so many participants and was indeed a great success.

A hundred and four authors from all over the world were able to present their papers and to discuss them with the audience.

An attractive social program gave the participants the opportunity to spend some time together in a relaxed atmosphere.

Unfortunately the reserved manner which is necessary for any research before its publication in special journals prevented the possibility to publish the most recent and probably interesting works in this book.

Giorgio A. Brunelli
Congress President 5th International Symposium on Experimental Spinal-Cord Repair and Regeneration and 1st AMN World Congress, Brescia, Italy

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Evidence based medicine in neurological rehabilitation – a critical review

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The concept of "evidence based medicine"

Over the last 20 years some magic words have delighted the neuroscientific community such as "plasticity" or "network". When it comes to medical services another magic word is "evidence based medicine".

Evidence based medicine (EBM) means to use well organized knowledge to shape decisions. This is of course a good idea. Historically the first roots of using knowledge to shape decisions goes back to the mid 18th century when d'Alembert and Diderot compiled knowledge in the "Encyclopedie" to enable "mankind" to marshal e.g. major political decisions on rational grounds. The first application of this evidence based principle in medicine is an essentially negative finding dating back to a paper by Pierre Louis in 1836 in which he disproved that blood letting was a cure for pneumonia. In the early seventies of the last century a group at McMaster University in Hamilton, Canada, came up with the idea to systematically collect knowledge in the medical scientific world in order to shape the decision behaviour of physicians.

Somewhat later Archie Cochrane in the United Kingdom suggested to compile "critical summaries" of randomised controlled clinical trials (RCT) to condense knowledge applicable to medical decisions.

Today no physician in the world would prescribe a drug unless he knows precisely about its possible efficacy shown by such RCTs and its possible side-effects.

Hence in drug research RCTs today are the gold standard for approval on world markets. Unless a particular new drug has been proven to be effective in RCTs in well-selected patient subgroups after passing toxicological and primarily clinical tests before, it will not be approved.

From this starting point the idea of RCTs, derived from drug research, has started to dominate the medical literature when it comes to approve or disprove certain interventions.

How far can principles of EBM practice be applied to training techniques in neurological rehabilitation?

Most "interventions" in neurological rehabilitation are training techniques and even today there is very little evidence of what is really "evidence based". In this review I will try to summarize the knowledge gathered in how far training techniques fulfil the criteria of evidence based practice.

Before we come to this point in detail some prejudices about the use of evidence based principles in rehabilitation should be ruled out: Evidence based medicine does not mean that the physician or the clinician in general cannot decide anymore what should be done in a particular patient. Evidence based elements are always only part of the entire decision making process to shape a custom tailored optimal approach for a particular patient.

Nevertheless nobody will deny that it is better to chose a particular training or teaching strategy which has been proven to be effective on a higher (see below) level of evidence rather than using an unproven technique.

The principle of evidence based medicine is based on the assessment of "quality" of studies trying to collect information about possible treatments. Today a hierarchical cascade of levels of evidence is used (see Table 1).

Similar to a hotel quality ranking these levels range from Ia down to level IV. Level Ia means that there exist metaanalyses summarising several of RCTs. Level Ib means that there is at least one RCT. The ranking goes down to lower quality levels to end with

Table 1. *Levels of evidence*

Ia:	Meta analysis of RCTs
Ib:	At least 1 RCT
IIa:	At least 1 controlled study – no randomisation
IIb:	At least 1 other type of good experimental study (e.g. pre-post)
III:	Good descriptive non-experimental studies (comparative, correlation, case)
IV:	Experts' reports, authoritative opinions

Table 2. *Rules for learning-oriented motor therapy*

- Task orientation
- Active behaviour
- Ecological validity
- Repetition
- Shaping
- Knowledge of results
- Motivation
- Competition

level IV, which may be somewhat depressant for an old-fashioned academic teacher in the sense that firm opinions and true beliefs have the lowest rank.

From confession to profession: changes in the paradigms of motor therapy

In neurological rehabilitation the treatment of motor problems, especially after stroke and brain injury, is one of the major targets.

After world war II certain physiotherapeutic ''schools'' have emerged and claimed how to treat the neurologically impaired patient. Neurodevelopmental treatment (NDT), the Bobath treatment [6], the Vojta treatment, the PNF treatment [118], the Brunstrom treatment [7] and many other treatments were described often linked to acronyms or individual person's names. Some of these schools claim to be based on a ''neurophysiological'' basis.

Looking closer at the supposed neurophysiological background, most of these schools seek their rules in spinal reflex physiology as summarized in Sherrington's book on the integrative action of the nervous system published in 1906. They do not however encompass the giant bulk of knowledge gathered in modern neurophysiology and neuroimaging.

A variety of studies have shown that none of these techniques has any superiority over each other when it comes to the effectiveness of treatment (e.g. 56, 57, 126). Even techniques theoretically based on contradictory principles have been shown to be similarly effective [119].

I will not deny that most of these motor therapeutic ''schools'' have collected elements of truth on empirical grounds. The only problem is that they have never proven that their particular intervention is useful or not.

Most of these classical ''schools'' of motor therapy were based on what could be called ''hands on''-treatment, i.e. making the therapist move or treat the patient. In contrast most of the EBM based models of therapeutic intervention are based on a ''hands off'' or ''coaching'' approach. This is not a trivial difference: For decades therapists have been teached to use their ''healing hands'' and hence have based the pride of their profession on ''hands on''-interventions. The therapist of the future however will be much more the ''coach'' of the patient using ''hands off''-interventions and consulting the patient what he or she can do *themselves*.

It has to be postulated that motor therapy of the 21 century should use knowledge collected in behavioural and brain sciences especially in the field of neuroplasticity and motor learning to deserve the term ''based on neurophysiology''.

Table 2 summarises some of elementary rules of motor learning based techniques and which are utilised in most of the evidence based therapeutic approaches which will be discussed below:

Training should be task oriented in the sense that the patient is trained on the desired target behaviour, e.g. the patient will only learn to walk when walking is trained and will only learn to grasp when grasping is trained. Furthermore the patient, whenever possible, should be challenged to work actively himself in an ecologically valid environment avoiding artificial environments. E.g. putting the patient on a training bench to facilitate ''truncal movements'' will not improve trunk or stance control unless the patient is ''advised'' to sit and stand by himself with vanishing support.

Repetition of a particular movement is one of the most elementary rules for the optimisation motor ranging from elementary force pulses to complex movement strategies. In the course of treatment the difficulty of the task should be gradually increased in order to keep up a challenge to the central nervous system as well as to keep motivation of the patient high. Conversely the task should not be too difficult in order to avoid frustration and demotivation.

Embedded into the training should be knowledge of movement and knowledge of results as major sources of feedback to consolidate the learned motor activity.

The motivation of the patient should always be kept on a very high level. It is unknown in how far competition between patients e.g. in training groups may also add to the therapeutic effectiveness. The motor therapists of the future will have to learn how to deal with such elementary rules and how to transport such rules into an everyday treatment environment. That means that also during their education knowledge about neuroplasticity and motor learning should be necessary parts of the their curricula.

Such motor learning rules of course can only be applied to a patient who has at least minimal voluntary motor activity and a minimum amount of attention span. In patients with severe levels of paralysis and reduced levels of consciousness learning rules are also applicable: But in these patients more "passive" elements of treatment have to be used including "hands on"-treatments, e.g. passive movement of extremity to avoid contractures and to facilitate the recovery of motor networks by reafferent feedback. Also for these procedures rules of motor learning have to be applied whenever possible.

Lessons from experimental neurobiology and neuroimaging

The progress in using non-invasive tools to study the human brain has brought considerable progress also to the field of interventional treatments: Today it is not a problem to look by non-invasive techniques in how the human brain e.g. after stroke reacts to certain interventions. The use of functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) has provided cues to understand what principles may underlie functional recovery [Classen 15, Liepert, 8–10, 28, 54, 69, 79, 121]. Today it is possible to analyse in individual patients the individual longitudinal dynamics of changes in cortical or subcortical activity in defined tasks after stroke or other brain injuries [68, 122, 123]. Also the use of transcranial magnet stimulation (TMS) helps to understand on an even shorter time scale how reorganisational principles work in the central nervous system (e.g. 12).

Taken together neuroimaging studies on brain reorganisation after brain injury show the following principal patterns [5]:

1. Areas adjunct to the impaired part of the cortex participate in reorganisation of function (perilesional plasticity)
2. Areas contralateral to the impaired cortical areas start to contribute to function (contralesional plasticity)
3. Areas far remote from the lesion contribute to recovery (multifocal plasticity)

Up to date we do not know in an individual patient which source of plasticity at what point in time can be exploited to facilitate recovery.

The longitudinal application of functional noneinvasive imaging techniques in brain recovery will open gates to look more closely at what happens in brain recovery and what particular intervention strategy can be helpful to facilitate functional recovery at a certain point in time after injury.

Examples of evidence based therapeutic intervention in motor rehabilitation

Table 3 summarises several of the techniques for the therapy of motor problems after upper motor neuron lesions for which higher levels of evidence have been published.

Before these procedures are addressed in detail it is important to state that we may not consider them to be "cook book-procedures" but general therapeutic rules.

It is interesting to note that for some of these evidence based therapeutic principles new guru – like attitudes seem to reappear which often resemble the behaviour of the classical "schools" of physiotherapy. In this respect the interested users of one or the other of these evidence based therapeutic techniques should always critically check in how far they will apply a

Table 3. *Examples of motor therapeutic techniques with higher levels of evidence*

– Treadmill training with partial body weight support (Ib)
– Constraint induced movement therapy ("forced use") (Ib)
– Functional electric stimulation (Ib)
– Repetitive training (Ib)
– Rhythmic acoustic stimulation (II)
– Imagery training (II)
– "Robot assisted training" upper extremity (Ib)
– Acupuncture as adjunct treatment (Ia)
– Force training (Ib)
– Changing sensory inputs
e.g. (plexus anaesthesia) (II)
(mesh glove stimulation) (II)

principle rather than a circumscribed procedure and may deliberately shape the use of this principle according to their individual patients' needs.

Treadmill training with partial body weight support

This treatment originated from work in patients with incomplete spinal cord injury at McGill University in Montreal in the group of Hughes Barbeau [5].

The underlying idea is that a patient with a central lesion and resulting impairment of gait takes advantage from the fact that locomotor activity is facilitated when the patient is put on a treadmill which urges the patient to step forwards. The neurobiological background of the procedure is not completely understood. It is argued that one of the major mechanisms will be the facilitation of so-called central pattern generators (CPGs) for locomotor behaviour which have been located on spinal level in experimental animals, especially cats, and which are probably located at brain stem level in humans.

Treadmill training is different from conventional gait training in the sense that it induces locomotor activity biomechanically not requiring the patient to initiate locomotion "voluntarily".

Treadmill training with partial body weight support has become a gold standard for gait training in patients with incomplete spinal injury originated by the work of Wernig [10, 20, 24, 127] and hemiparesis after stroke [1, 4, 18, 22, 31, 33–37, 65, 71, 80, 100, 114] and in children with cerebral palsy following the germinal Study by Hesse and workers 1994 [86].

There are so far no really confirmed rules about the dosage or shaping of treadmill treatment (e.g. when to increase the speed of the treadmill, when to lower the weight support etc.).

Constraint induced movement therapy (forced use training)

It was an important observation made by E. Taub in monkeys that hemiparetic animals improved faster and to greater extent when they were "urged" to use the affected side by immobilisation of the unaffected side [102]. After animal experimental studies in primates became more and more difficult for ethical reasons, Taub and his colleagues decided to apply these findings to stroke patients with immense success [103, 104].

Since constraint induced movement therapy (CMT) or, as I prefer to call it, "forced use"-treatment has become a beautiful example for a rapid transfer of neurobiological thinking into a real therapeutic approach. The basic idea is that forcing a hemiparetic patient to use the affected side by immobilising the non-affected side by more or less drastical measures (gloves up to casts) inforces reorganisation in the central system and avoids so-called "learned non use".

Clinical studies have shown that this type of treatment is effective in adults after stroke [30, 48, 63, 97, 104, 105] and also in children with hemiparetic problems [19, 103, 129]. Almost monthly new papers are added to the literature indicating the usefulness of this principle. It is however important to state that we are dealing with a therapeutic principle rather than a therapeutic technique.

The "inventors" of this technique nowadays seem to become "ideological" about the minimum amount of time which the unaffected side has to be immobilized or for how long the affected side has to be trained during the day (6 hours and more).

However more and more studies show that also a more "liberal" handling of the constraints show similar results [76, 109]. The ideal patient in whom this therapeutic principle can be applied has a hemiparetic problem but residual proximal and distal motor abilities so that he is able to move the extremity to some extent. The patient is then involved into a protocol with part time immobilisation of the good side and asked to work with the affected side for a certain amount of time during the day in which he should use the affected side in a well-shaped way in an "enriched" environment. Well-shaped means that the amount of difficulty to fulfil the task demands is gradually increased by the therapist in a way that the patient is just able to do a particular task and the difficulty can be slowly build up following possible improvements of the patient.

Originally this technique has been applied primarily in patients with chronic hemiparesis after stroke, i.e. 3 and more months after the insult. The reason for this was to avoid contamination of possible results with spontaneous recovery to demonstrate the usefulness of the procedure. Nevertheless the technique can also be applied successfully to patients in more acute states after stroke.

Functional imaging studies have shown that during CMT well-organized pattern of cortical involvement

can be observed [45, 53, 85] underlining that this technique induces brain plasticity.

For patients with moderate to mild hemiparetic problems CMT is on the way of becoming a standard therapy. The rules of application vary from center to center. However data about dose-response relationship for this training, i.e. how many hours the good side has to be immobilized or how many hours the affected side should be used etc., are missing.

It is also not clear if the major effect of CMT is caused by the *usage* of the affected side or the *immobilisation* of the non-affected side. Recent data applying plexus anaesthesia to the non-affected side [27] suggest that immobilisation may be the major factor. It is most likely however that the combination of reducing competitive inputs from the unaffected and training the affected side yield the maximal reorganisation response.

Functional electric stimulation (FES)

After upper motor neuron lesions there is only little if any denervation of involved muscles. That allows to stimulate the affected muscles electrically to yield good contractions and movements on the paretic side. This results in afferent signals towards the involved motor networks of the affected extremity and may induce reorganisation of motor control networks.

Electrical stimulation is especially useful in patients with severe paresis at a stage they have still no ability for voluntary contraction [39, 41, 46, 47, 67, 106]. In these patients the repertoire of possible effective interventions is very limited. Electric stimulation can be combined with EMG-biofeedback to further improve the therapeutic results [38]. It is not really known by which mechanism this technique works but in patients with severe paretic problems it is a good choice to try. We observe that patients having been trained with electrical stimulation may recover to an extent that, in the next step, they can be enrolled in e.g. a ''forced use'' treatment.

It is unclear which dosis of electrical stimulation during the day is most effective. Again, more work is necessary to develop this principle further.

Repetitive training

Repetitive training is a major general principle for functional reorganisation. In normals it has been shown that for certain skills as for instance rolling cigars the optimisation of movement trajectories is dependent on the number of repetitions up to millions [16]. Repetitive training does however not install a ''new'' motor program but helps to refine it. Of course most patients with problems have to refine trajectories. From this point of view it is clear that the aspect of repetition is generally helpful to improve newly learned motor programs in paretic patients. Repetitive training however can be expected to be useless, when the patient has not yet been able to reestablish a concept of a trajectory. Such a concept or a ''motor program'' could be reinstalled by e.g. imagery learning (see below).

The study by Bütefisch *et al.* (1995) [11] was the first supporting the idea of repetitive training in an isometric force production task in the upper extremity. Numerous studies since have shown that the idea of repetition is a useful therapeutic tool in lower and upper extremity motor therapy [82, 84, 96, 98, 130]. Again it has to be noted that repetitive treatment is not a therapeutic procedure but a therapeutic principle.

Rhythmic acoustic stimulation

Rhythmic acoustic stimulation (RAS) is another therapeutic principle. It has been primarily developed by work from the laboratory of M. Thaut at Colorado State University. The basic idea is that rhythmic movements can be facilitated by an intraining coupling with a sensory repetitive rhythmical signal. This group has shown that RAS is helpful in improving motor function in patients with locomotor problems (e.g. in Parkinson's disease, Huntington's disease and after stroke [108–111]) as well as in upper extremity problems [107]. The precise neurobiological mechanism of how the brain responses to rhythmical input is not entirely clear. Recent neuroimaging studies however show clearly parietal and frontal areas being involved in the processing of rhythmicity [95]. RAS is also a nice example of how a ''soft'' discipline as ''music therapy'' can be converted into a tough and scientifically well-grounded element of motor therapy.

Mental training

Motor training by imagery or imitation is one of the most interesting ways of thinking about applying motor learning rules to motor rehabilitation. Over the last decade imagery studies have shown that motor behaviour in normals and also in patients with a variety of

neurological problems including Parkinson's disease and stroke can benefit from a ''non-hands on'' pure imagery training.

Several groups have addressed the neurobiological mechanisms underlying learning by imagery and learning by imitation [60, 61, 81, 88, 89, 94, 131–133]. The bottom line is that a variety of parietal and frontal networks of either hemisphere participate in generation of movement trajectories if they are ''really'' performed or merely imaginated.

Motor learning by imagery and its application to motor rehabilitation is still in its infancy but the available data suggest that such techniques in combination with other offers new avenues to reestablish movement trajectories also in severely affected patients. To whom it is to early to apply trajectorial refinement approaches such as ''repetitive training'' or forced use treatment. It is however unclear which subgroups of patients are most likely to respond to such an approach.

Force training

Training of elementary force can also be a helpful tool in the treatment of patients with central motor problems. It is well-known that strength training is useful to facilitate recovery of motor function after peripheral nerve injuries.

Nevertheless force training can also be applicable to patients with upper motor neuron lesions. This has been shown in hemiparesis after stroke [90, 125] as well as in cerebral palsy [Damiano *et al.* 2002, 17].

Robot assisted upper extremity training

Over the last decade robot devices have been developed to add to the therapeutic portfolio in neurological patients. It has been proven that especially in patients with severe paretic problems the use of shoulder-elbow and wrist robots [23, 25, 115–117] is useful. Whereas ''active'' treatment strategies such as ''forced'' use or ''repetitive'' or ''force'' training can be applied only to a patient who has at least limited access to voluntary control these robot techniques can be applied also to the completely plegic patient. Similar to functional electric stimulation the robot always guides the patient to the desired target for an elbow or wrist movement. With the patient gaining more and more voluntary control the robot gradually reduces the assistance. The robot sensors can be extremely sensitive and hence the patient-robot interaction is more effective than a patient-therapist interaction because a therapist can never be as sensitive as the sensors of the robots and the timing and shaping of assistance by the therapist can never be as finely tuned as the assistance provided by the robot.

In this respect the use of robots for upper extremity motor control treatment documents that a man-machine interaction can result in a ''quantum step'' which can never be done by a therapist-patient interaction. This is similar to the treadmill training situation (see above).

Changing sensory inputs

Changing sensory inputs to the affected or non-affected side in patients with e.g. hemiparetic problems becomes an interesting tool to shape brain recovery: Numerous studies have shown that changes of the afferent input give rise to a change in the cortical representation measured by functional imaging techniques as well as documented by therapeutic benefits [e.g. 99, 134, 135].

A variety of manipulation of sensory inputs has been used such as tactile or electrical stimuli applied to fingers by ring electrodes or subthreshold electrical stimulation applied by whole hand (mesh glove) intervention.

An interesting new approach has been the use of selective anaesthesiological blockades of the proximal part of the arm plexus in patients with good proximal but bad distal arm function. The paper by Muellbacher *et al.* [66] was the first to show that in chronic stroke patients with distal hand paresis a transient blockade of the shoulder/elbow muscles and sensation may result in even permanent improvement of distal motor function.

This is an elegant example in how far knowledge about reorganisation in cortical representation areas after peripheral blockades or amputations as originated by the work of Merzenich and Jenkins at UCSF [58, 59] has penetrated into a therapeutic approach. In our hands such blockade techniques appear to be useful also in patients with more acute stroke problems. As mentioned earlier the blockade of the arm plexus of the intact side in hemiparetic patients may also facilitate recovery of the affected side [27].

Acupuncture

Acupuncture is certainly not a classical school medicine technique and is often listed under ''traditional

chinese medicine'' or other paramedical approaches. Nevertheless, and that is also a lesson to be learned from evidence based medicine acupuncture even in meta-analysis has been shown to be effective at least as an adjunct therapy to improve motor function after stroke and spasticity e.g. [26, 42, 52, 64, 77, 101].

Evidence based assessment of therapeutic efficacy is blind to knowledge about mechanisms of interventions. It is very important to note: Similar to the fact that we have no idea how many pharmacological agents work, when their efficacy and safety have been proven we are prepared to use them for a particular target. We should look at training interventions in a very similar way.

Dosage of treatment

There exist only few studies addressing the question which is the optimal dosage e.g. of physiotherapy in particular patients. The few available studies are in favour attending that ''more'' therapy yields somewhat better results [49–51].

Table 4. *Problem: impairment of distal hand|wrist paresis e.g. after stroke*

Step 1	
Status:	plegic hand
Measures:	repetitive passive movement
	FES
	robot assisted therapy
	sensory manipulation
	upper plexus anaesthesia, electric or vibratory
	subthreshold finger stimulation, etc.
Step 2	
Status:	minimal voluntary activity
Measures:	FES
	robot assisted therapy
	mental training
	repetitive training of first possible elementary movements
Step 3	
Status:	gross voluntary movements
Measures:	forced use
	mental training
Step 4	
Status:	improving dexterity
Measures:	well-shaped ADL and writing training
	forced use

Towards guidelines: which therapy for which patient?

Which regimen from the repertoire of therapeutic techniques mentioned above should be applied to a particular patient, at which status of recovery e.g. after a cerebral infarction? What we have to work out in the future certainly are guidelines stating what particular treatment can be used in a particular patient depending on the functional status.

Table 4 provides a provisional proposal which therapeutic procedures should be used in a patient with upper extremity weakness after stroke using the before mentioned EBM-based procedures starting from complete plegia of the hand to better levels of function. In the plegic state the application of passive movements, FES and external stimulation such as tapping or electrical stimuli can be used. In the next step when the patient first shows some voluntary activity the therapist can go on with FES and may use mental training such as imagery and rhythmic acoustical stimulation as well as starting with repetitive training of those trajectories the patient is just able to do. Furthermore a shaping program of learning new trajectories can be installed.

In the next step when the patient shows limited but clear voluntary motor activity a forced use shaped training approach with added rhythmic acoustical stimulation and force training can be used. Finally when the patient reassumes some degree of dexterity a group oriented repetitive shaped training approach for fine motor control and writing, when the dominating side is involved, can be used.

Hence depending on the actual motor status of the patient, different effective settings can be used in sequence. It is open however to define clearly what are the preconditions to define the transition from one to the other form of treatment and also what dosage is optimal to guide the patient from one step to the next. Similar hierarchical rules could be defined for the training of grasping function or locomotion.

What design of studies?

Following the framework of EBM we certainly need more studies to address the efficacy of treatments. There is however a plethora of problems in designing, organising and conducting such studies. It is difficult to define who will be the financial sponsor for such studies: Today it is a multimillion dollar enterprise just to find out if a dose of 50 or 100 mg of salicylates is more effective as a secondary prophylaxis after stroke or myocardial infarction. Such studies are usually covered by pharmaceutic companies who have an interest in selling their products. The situation is com-

pletely different for therapeutic intervention studies in rehabilitation: We will probably never be able to recruit the numbers of patients typical for pharmacological studies and we will also be unable to find the sponsors considering the fact that training techniques cannot be converted into sellable products.

Many of the studies cited above suffer from severe limitations: Often the samples are small, inclusion and exclusion criteria are strict and the used therapeutic approaches are not described in sufficient detail.

It often remains unclear if the study was designed to find out *how* a particular strategy works or *if* a particular strategy works. To find out how a particular strategy works necessarily more rigid inclusion-exclusion criteria are needed resulting in limited numbers of patients who can be enrolled. On the other hand we need studies addressing the issue if a certain strategy is efficacious in patients really existing in everyday life. Too strict inclusion-exclusion criteria limit the number of patients to be enrolled in such a study. We are often faced with the situation, that we start with possibly hundreds of target patients, which melt down to very few in the end, due to inappropriate inclusion criteria with the consequence that a therapeutic technique may be evaluated working only in patients who are virtually not existing. Studies must enrol the *typical* patients a rehabilitative neurologist is faced with day by day. Too rigid inclusion criteria will limit studies to an extent, that they will not address the real patient anymore and hence may, even if they are beautifully designed, not give real answers what to do with the day by day patient. In future we have to separate out intellectually what a study is aiming at.

Furthermore such efficacy oriented studies have to describe in detail which therapeutic strategy has been used, e.g. stating the sort of training material, the shaping rules for increasing task difficulty, and the amount of the time the patient is treated etc.. Many of the a.m. studies have used ''add on'' treatments, e.g. using one or the other learning oriented technique in addition to ''conventional'' therapy. Such a design is usually chosen for ethical reasons, arguing that ''conventional'' treatments still are the absolute minimum a patient deserves. On the other hand all ''add on''-designs have to ascertain that the patient in the ''treatment'' compared to the ''control'' group has been attributed the same amount of time by the therapist, e.g. by using sham treatments, to ascertain, that equal time attributed to the patient in control and experimental groups. In summary we need studies applicable to real patients with techniques sufficiently described in detail so that they can be used in following studies and can be selected by clinicians who want to use them.

What about cognitive rehabilitation?

The data based for rehabilitative techniques in cognitive cerebral rehabilitation is much smaller than for the rehabilitation of motor problems.

Most of the used therapeutic techniques have not more than level II EBM. The European Federation of Neurological Societies has recently compiled a sort of guidelines for cognitive rehabilitation [15].

Another critical summary on evidence based principles in cognitive rehabilitation has been put together by Cicerone *et al.* (2000) [14].

We recently did an extensive medline literature research recovering the decade between 1994 and 2003 using as key items: attention, concentration, executive functions, memory and cognitive rehabilitation.

This resulted in 780 published articles on this issue. I68 of these studies were randomised controlled studies. Reducing the data based on those studies with patients with either traumatic brain injury or stroke and taking out those studies with pharmacological intervention and studies in either paediatric or geriatric population (below 18 or above 75 years age) resulted in only 13 remaining RCTs (EBM-level Ib).

4 Studies addressed problems of attention deficits [Amos, [2], Sohlberg, [92]]. Memory deficits were addressed in another 4 studies [21, 75, 112]. One study shows the benefits of computerized reading training in aphasia [Katz and Wertz, 44]. In patients with visual neglect after stroke visual scanning procedures [2] proved to be useful. Another study [3] showed that a neglect training approach using the training of functional abilities was superior over conventional treatment forms [43]. Furthermore a visuo-spatial reconditioning technique using both visual and proprioceptor biofeedback proved useful in neglect patients [128] as well as prism adaptation [83].

It is obvious that it is a very small bulk of evidence collected so far and certainly much more studies are necessary to address possible efficacies avenues in cognitive rehabilitation.

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Quality management in traumatic brain injury (TBI) Lessons from the prospective study in 6.800 patients after acute TBI in respect of neurorehabilitation

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Summary

Preliminary results on epidemiology, acute hospital care, and neurorehabilitation of TBI are presented of the first ever prospective controlled German study to analyse the use of regional structures and quality management as provided by the German social healthcare system. The sum of inhabitants in Hannover and Münster area was 2,114 million. Within an area of 100 kilometres diameter each. 6.783 acute TBI (58% male) were admitted for acute treatment from March 2000 to 2001. Definition of acute TBI was according to the ICD 10 S-02, S-04, S-06, S-07, S-09 in combination with dizziness or vomiting; retrograde or anterograde amnesia, impaired consciousness, skull fracture, and/or focal neurological impairment. The incidence was 321/100.000 population. Cause of TBI was traffic accident in 26%, during leisure time 35%, at home 30% and at work 15%. Initial GCS (emergency room) was only assessed in 3.731 TBI (=55%). Out of those 3.395 = 90,9% were mild, 145 = 3,9% were moderate, and 191 = 5,2% severe TBI. 28% of 6.783 patients were <1 to 15 years, 18% > 65 years of age. The number admitted to hospital treatment is 5.221 = 77%, of whom 72 patients (=1,4%) died caused by TBI. One year follow-up in 4.307 TBI patients (=63.5%) revealed that only 258 patients (=3,8%) received neurorehabilitation (73% male), but 68% within one month of injury. Five percent of these patients were <16 years of age, 25% > 65 years. Early rehabilitation "B" was performed in 100 patients (=39%), 19% within one week following TBI. The management of frequent complications in 148 patients (=57%) and the high number of one or more different consultations (n = 196) confirmed the author's concept for *early neurosurgical rehabilitation* in TBI when rehabilitation centres were compared regarding GCS and GOS: Early GOS 1 = 4%; GOS 2 = 2,7%, GOS 3 = 37,3%, GOS 4 = 26,7%, GOS 5 = 29,3%, final GOS scores were 1 = 1,2%, 2 = 1,7%, 3 = 21,8%, 4 = 36,2%, and 5 = 39,1% of all patients at the end of rehabilitation. Mean duration for both "B" and "C" was 41 days compared to 80 days for "D" and "E". An assessment of both GCS and GOS was insufficient (Fig. 1).

Keywords: Epidemiology; traumatic brain injury; prospective controlled clinical study; complications; polytrauma; TBI Guidelines; posttraumatic functional rehabilitation; early rehabilitation; neuropsychological sequelae; quality management; German social and healthcare system; quality of life.

Introduction

Acute traumatic brain injury (TBI) is a major ethical and social burden in industrialized countries with regard to life-long disability, unnatural death, and the enormous socio-economic costs. The costs have to be covered by the national social and healthcare systems together with the care providers and care givers regarding accident prevention, acute medical care, and social reintegration of the victims. Traffic accidents are known to cause most of the TBI-related deaths and disabilities, mainly among the younger population between 20 and 30 years [1, 2, 7–11, 13–15, 19, 23, 24].

The German social and healthcare systems today provide an exemplary high standard of structural and process quality for the medical management of acute TBI, aimed at the victim's full social reintegration [7, 8, 14–18]. *Holistic* rehabilitation means an ongoing chain of functional neurorehabilitation that starts already at the site of the accident, with resuscitation of vital body functions, acute treatment, and restoration of the impaired higher nervous functions, proper treatment and, respectively, prevention of primary and/or secondary complications [3, 4, 12–14, 21, 22]. This applies to both the body as well as to the victim's body-related structures (WHO-JCF classification) according to the *Spectrum of functional neurological-neurosurgical neurorehabilitation* [16]. Since the wearing of helmets for motorcyclists and the use of safety belts also for passengers occupying the rear seats of vehicles has become compulsory by law and specially designed safety seats for babies and small children are available, there has been a significant reduction in the number of severe and fatal TBI accidents in Germany and Austria [1, 2, 11]. In addition, modern techniques for road safety and speed limits in dangerous areas have also been quite successful in TBI prevention, although very costly. This is reported both for isolated TBI and cases of polytrauma regarding all traffic participants as published in the official governmental annual books of statistics in Germany [2, 6].

National and international guidelines for the acute management of TBI have become widely accepted and are being followed today, with some minor local modifications according to the experience of regional scientific experts such as intensive-care physicians, trauma- and neurosurgeons [3, 4, 11–14, 19, 21]. The senior author and two other participants of our study group, W. Bock and E. Rickels, actively took part in editing some of these guidelines and recommendations as well as in the planning of new structures for trauma care and neurorehabilitation, for example the Governmental Task Force of North Rhine-Westphalia [7], the interdisciplinary Task Force on ENNR [16, 24], and the recommendations for management of acute trauma care and for posttraumatic intracranial pressure of DIVI [4]. The network of regional structures for public healthcare are state-of-the-art throughout Germany, and they are also reported to be on a high standard level in Austria [1, 2, 11, 18, 21, 22]. The same should be true for quality management of posttraumatic functional neurorehabilitation with regard to the different design of institutions and specialized personnel, which is based on the philosophy of inter- and multidisciplinary team approach and treatment for all phases of neurorehabilitation: the (acute) early and, when necessary, continuous rehabilitation described as acute phase (''B''), post-acute (''C'') and long lasting phases ''D'', ''E'', as well as for outpatient rehabilitation ''F'' [6, 10, 11, 16–18, 20, 24]. This could be achieved owing to the close cooperation of politicians, care providers, and care givers together with expert physicians for neurorehabilitation and neuropsychology, although special guidelines for neurorehabilitation have not yet been published in Germany or in other Western countries. In Germany we are pursuing mainly the structural and management quality for functional neurorehabilitation as recommended by the expert opinion of the German Task Force for early neurological-neurosurgical rehabilitation (ENNR) in 1993 [16, 24].

Bearing this in mind it is surprising that even in Germany there is a lack of reliable figures for acute TBI care and posttraumatic functional neurorehabilitation to evaluate and qualify the efficiency of the regional structures and the medical treatment of TBI. This was the reason for carrying out the first controlled prospective multicentre study in two regions, where a sufficiently high number of TBI victims within one year could be anticipated to statistically evaluate the actual quality management with respect to acute treatment, neurorehabilitation, and early outcome in Germany.

Material and methods

The purpose of the clinical prospective controlled multicentre study was to analyse the epidemiology and quality management of acute medical care and posttraumatic functional neurorehabilitation within one year. One of the authors (E. Rickels) planned to use the data as a pilot study for a German TBI database while the senior author (K. von Wild) was especially interested in all questions regarding quality management in posttraumatic rehabilitation.

The initiative, both authors derived from this, was focused on two comparable regions because of their intensive personal experience in the acute management of neurotrauma care and rehabilitation as well as of the insight into regional structures. The catchment area was 2.114.385 inhabitants. In the Hannover region, the capital town of Lower Saxony and an industrialized urban region, there were 1,256.618 million inhabitants, and in the Münster region, the governmental capital of North Rhine-Westphalia, rural, with 858.767 population, each with a geographical diameter of 100 km.*

Both cities have major trauma centres and neurosurgical depart-

* Data from the Statistische Landesämter Niedersachsen und Nordrhein-Westfalen and Statistisches Bundesamt per 31.12. 2000.

ments at the medical faculty of the respective universities and at the city hospitals with maximum trauma care (type A) ready for TBI besides another 13 local hospitals each. For posttraumatic neurorehabilitation 28 institutions are available for both areas.

Three special forms have been designed by the TBI Study Council. They contained special queries on documentation of (I) first aid and acute trauma care, (II) hospitalisation, and (III) posttraumatic neurorehabilitation "B" and "C" to "F", and (IV) telephone interview at the end of the first year follow-up according to standard medical examination and standard classification criteria being the GCS[a] AIS-ISS[b], CRS[c], FIM[d], FRBI[e], GOS[f].

The three questionnaires (No I–III) were introduced to the physicians responsible for documentation at the respective hospital and a pilot study was first performed in both regions to review practicability and reliability. The project was evaluated and approved by the Ethical Committee of Medizinische Hochschule Hannover. Between March 1, 2000 and February 28, 2001, the study was conducted by collecting data of all patients admitted to one of the 30 hospitals based on the medical history of having sustained an acute isolated or combined TBI of any severity range (GCS 15-3).

The definition of acute TBI was made according to the ICD-10 S 02, S 04, S 06, S 07, and S 09 in combination with at least two out of the following complaints: dizziness or vomiting; retrograde or anterograde amnesia; impaired consciousness; skull fracture; and/or focal neurological impairment.

The early outcome was evaluated as GOS at the end of hospital medical treatment and/or at the end of early ("B") and long lasting rehabilitation ("C"-"F"), while social follow-up was done by telephone interview after one year. Data collection was supervised by the Centre of Quality management in Healthcare and statistically analysed by the second author (Paul Wenzlaff) in close cooperation with the Study Council.

Results

The data presented were recorded in February 2004. Within one year a total of 6.817 head injured patients were listed. 6.783 TBI patients (58% male) with completed files were admitted to one of 14 out of 15 hospitals in Hannover and to 13 of 15 in Münster, respectively, with recruitment of 67% of TBI patients in Hannover and 33% in Münster. The incidence of TBI for both regions was 321/100.000 population calculated for 6.783 completely documented TBI patients (Hannover 370/100.000 versus Münster 249/100.000 population) .

Initial GCS following the emergency examination < 1 h after injury was only assessed in 3.731 (=55,0%) out of 6.783 patients. This subpopulation has 330 "mild", 14 "moderate", and 19 "severe" cases of TBI per 100.000 population. The distribution of gender and of age groups (Figure 1) showed some differences when compared to the German population (shown in parentheses) as they were 12,7% (5,2%) TBI patients < 1 to 5 years; 28,1% (16,5%) TBI patients < 1 to 15 years; 17,7% (17,35%) TBI patients > 65 years, and 10,8% (7,7%) TBI patients > 75 years. 5.221(=77%) of acute TBI patients were hospitalised. Complete files could be analysed for 6.783 patients with one year follow-up by telephone interview of 4.307 patients (=63,5%). At the first clinical examination < 1 h after injury, the GCS was assessed in only 3.731 of the patients (55%): 90,9% = "mild", 3,9% = "moderate", 5,2% = "severe" cases of TBI (Table 1). When classified according to posttraumatic impairment of consciousness and awareness, figures showed "orientated" patients in 74% of all cases of TBI, while 18% of the TBI patients had "impaired consciousness", 1,4% were "comatose", and 3,6% were "anaesthetized"; data were not available for 3,2% of all patients with TBI.

Causes of TBI included injuries sustained while pursuing leisure-time activities in 35,3%, injuries at home in 29,8%, traffic injuries in 26,1%, and injuries suffered at the workplace in 14,9%, respectively. With regard to age groups due to sports and violence (in parentheses), we observed acute TBI in <16 years = 12,6% (9,95%), in >65 years = 0,4% (2,2%),

Table 1. *Cause of TBI and TBI severity as assessed with GCS at the Hospital's emergency room examination in N = 3731 patients (=50.1%) while in 3.037 TBI (=49,9%) data were missed Manifold naming regarding the causes explain the differences in the sum of numbers in the vertical columns*

GCS	15-13	12-9	8-3	Missing	Total N
Traffic accident	841	47	113	772	1.773
	84%	4.7%	11.3%	–	100%
Leisure time	1.257	50	36	1.054	2.397
	93.5%	3.7%	2.6%	–	100%
At work	524	16	14	457	1.011
	94.6%	2.9%	2.5%	–	100%
At home	1.023	41	41	913	2.018
	92.6%	3.7%	3.7%	–	100%
No special	3	1	1	23	28
cause	60	20%	20%	–	100%
no data	5	1	–	54	60
	83%	17%	–	–	100%
All	3.395	145	191	3.052	6.783
	90.9%	3.9%	5.2%	(=45%)	100%
				–	

[a] Glasgow Coma Scale Teasdale G., Jennett B. (1974) in Lancet 2, 81–84, and adopted for children by Ritz A. *et al.* (1982) in V. v. Loewenich (ed) Pädiatrische Intensivmedizin, Thieme pp. 19–25, [b] Abbreviated Injury Scale and Injury-Severity Score Greenspan L. *et al.* (1985) J Trauma 25, 1, 60–64, Iss Baker S. P., O'Beil B. (1976) J Trauma 16, 882–85, [c] Coma Remission Scale [11, 13], [d] Functional Independence Measure Heinemann A. *et al.* (1994) Arch Phys Med. Rehabil 75, 127–132, [e] Schönle P. W. (1996) Neurol Rehabil 1, 21–25, [f] Glasgow Outcome Scale Jennett B., Bond M. (1975) Lancet 1, 480–484.

and >75 years 0,3% (1,1%), due to falls and to traffic accidents (in parentheses), <16 years 62,7% (13,1%), >65 years = 80,9% (13,5%), and >75 years = 87% (8,6%) of all cases of TBI.

An open fracture was diagnosed in 2,8% of TBI patients. Combined trauma of TBI with multiple organ lesions was diagnosed in 75% of patients, with 53,6% facial injuries, 18,2% limb injuries, 8,1% cervical-spine injuries, 6,6% injuries of the thorax, 3,1% of the pelvis, 2,4% of the spine, 2,4% abdominal lesions, and of other parts of the body in 24,9%, while no data were available for 7,8% of the total number of TBI cases (indication of multiple lesions is possible). Seventy eight percent of all patients were admitted to the departments of trauma and/or general surgery, 7% for maxillofacial surgery, 4% for neurosurgery, 3% to paediatric clinics, 1% to neurology, and 7% to others. Evidence of alcohol was given in 16,7% of all cases and of drugs in 8%. Early outcome: 38% GOS 5, 36% GOS 4, 21% GOS 3, 2% GOS 2 (VS), 1% GOS 1.

One-year follow-up was done in 4.525 TBI (=66,7% out of all TBI victims) of which 4.307 (=63,5%) were assessed by questionnaire or by standardized telephone interview.

Out of all 5.221 patients that were hospitalised for medical treatment 90% were discharged directly to their home, 3.925 of them with special recommendation for additional medical treatment or diagnostics, 749 patients without any special recommendation. Sixty-nine patients were admitted for early rehabilitation, another 184 to a common rehabilitation institute, 86 victims were transferred to another hospital, 113 to a nursing home, and 19 for home care. Forty-four inpatients died. Data are missing for 32 out of all 5.221 hospitalised patients (Table 2). At that time of discharge 4.644 patients (=89%) were fully ambulant, 348 patients (=6,7%) partially mobilized, and 109 patients (=2,2%) immobile, while data were not available for 119 patients (=2.3%). Regarding awareness and cognitive orientation at the time of discharge, 4.858 patients (=93,1%) were orientated, 192 patients (=3,7%) were disorientated, with data not available for 170 TBI patients (=3,3%).

Table 2. *Discharge after acute hospital treatment as compared to initial GCS N = 5.221 patients*

Discharge	Mild	Moderate	Severe	No	All
Home with special recommendations	3.576 91.1%	272 6.9%	2 0.1%	75 1.9%	3.925 100.0%
Home without recommendations	695 92.8%	45 6.0%	1 0.1%	8 1.1%	749 100.0%
Early neuro-rehabilitation	14 20.3%	8 11.6%	2 2.9%	45 65.2%	69 100.0%
Rehabilitation	108 58.7%	47 25.5%	2 1.1%	27 14.7%	184 100.0%
Other hospital (no rehabilitation)	59 68.6%	12 14.0%	1 1.2%	14 16.2%	86 1.6%
Nursing home	93 82.3%	15 13.3%	1 0.9%	4 3.5%	113 100%
Home care (completely dependent)	17 89.5%	2 10.5%	–	–	19 100%
Death	6 13.6%	–	–	38 86.4%	44 100%
Missing data	13 40.6%	4 12.5%	~	15 46.9%	32 100%
Total number	4.581 87.7%	405 7.8%	9 0.2%	226 4.3%	5.221 100.0%

Neurorehabilitation

A total of 258 patients, out of 6.783 TBI, 73% male and 27% female, were admitted for neurorehabilitation, 142 (=55%) in the Hannover region out of 4.643 patients (=3,1%) with TBI compared to 116 patients (=45%) in the Münster region out of 2.100 (=5,4%) TBI patients. Thirteen patients, 10 from the Hannover area, were younger than 15 years (=5%) while 63 patients (=24,4%) were older than 65 years, 21,2% in the Hannover area and 31% in the Münster region, respectively. From acute hospital admissions 251 patients (=97,3%) were directly admitted while six patients (=2,3%) came from an early-rehabilitation unit (phase B for further rehabilitation phases C, D, and F), and one TBI patient (0,4%) from a nursing home. In 175 patients (=68%) admission occurred within one month, in 60 patients (=23%) between one and three months, and in three victims (=1,2%) between three and six months following TBI injury. BI was seen in association with other injuries in 95 patients (=37%); 10 patients (=3,9%) suffered from TBI combined with a spinal injury, half of them sustained polytrauma.

TBI severity was assessed at the beginning of rehabilitation in 175 TBI patients (i.e. 68% out of a total of 258 patients) as being mild in 115 patients (=66%), moderate in 41 patients (=23,4%), and severe in TBI 19 patients (=10,9%) (Tables 7, 8). Worth mentioning here is the fact that at the first emergency examination (at hospital), only 41 out of these 258 patients (=16%) had mild TBI, 29 patients (=11.2%) moderate TBI, and 87 patients (=34%) suffered from severe TBI while 101 patients (=39%) were not classified.

Table 3. *TBI severity (GCS) at the beginning of early rehabilitation differentiated by regions*

GCS	MS	H	Else	Total	%
Mild	23.4%	0.0%	20.0%	19	19.0
Moderate	10.9%	0.0%	10.0%	9	9.0
Severe	29.7%	50.0%	55.0%	38	38.0
Not assessed	35.9%	50.0%	15.0%	34	34.0
All	64	16	20	100	100.0
	100.0%	100.0%	100.0%		

Table 4. *Time interval between accident and admission for early rehabilitation. N = 100 Pts*

Time interval/ days	MS-CL	MS-CL and other hospitals	H main centre	Other hospitals	Total	(%)
1.–7.	16	2	0	1	19	19.0%
8.–14.	9	4	2	2	17	17.0%
15.–21.	15	3	5	2	25	25.0%
22.–30.	7	3	4	7	21	21.0%
30.–90.	5	0	5	7	17	17.0%
91.–180.	0	0	0	1	1	1.0%
All	52	12	16	20	100	100.0%

Early neurorehabilitation (ENNR) (Tables 3 and 4)

A total of 100 patients (=39%) of the 258 TBI cases were admitted for ENNR (phase B). The time interval between the accident and admission for ENNR showed marked differences between the main rehabilitation centres in Münster, in the Hannover region, and other units. Only 76 of them were initially assessed with GCS, in 19% suffering from mild, 9% moderate, and 38% severe TBI. Early Rehabilitation Barthel Index (ERBI) [17] obtained from 258 patients was reported as being −325 to +25 in 150 TBI patients (=58,1%), +26 to +74 in 29 patients (=11,2%), and >75 in 25 patients (=9,7%) , but no data was available for 54 patients (20,9%). Signs and symptoms of severe central disturbances were present as fever in 46 of 258 patients (=18%), vegetative disorders in 99 patients (=38%), sweat in 84 patients (=33%), salivation in 72 patients (=28%), and swallowing disorders in 84 patients (=33%), while spastic condition was present in 45 patients (=17,4%), contractions in eight patients (3,1%), and pressure ulcer in 24 patients (=9,3%).

Complications

Complications occurring during rehabilitation were documented in 110 patients (=42,6%), internal complications developed in 71 patients (=27,5%), the most frequently recorded complications were of pulmonary nature in 57 patients (=22%) compared to intestinal in 15 patients (=5,8%) and cardiovascular in 13 patients (=5%) as well as other internal complications. Taking second place were urinary complications in 45 patients (=17,4%) followed by neurological-neurosurgical complications in 39 patients (=15,1%).

Ophthalmic complications were seen in 23 patients (=8,9%). Accordingly a high number of consultations were necessary during rehabilitation, 118 for ophthalmic causes (=60%), 114 for ENT (=58%), internal medicine for 97 patients (=50%), microbiology lab investigations for 103 patients (=53%), neurological consultations were necessary in 73 patients (=37%), for traumatic incidents in 62 patients (=32%), neurosurgical for 40 patients (=20%), abdominal surgery 16 patients (=8%), maxillofacial surgery 15 patients (=8%), for urological in 11 patients (=6%), paediatric in 6 patients (=3%), gynaecological in 2 patients (=1%), and for others in 17 patients (=9%). Ninety-two out of 196 patients (=47%) were examined at least once by an ophthalmologist and an ENT specialist, while other combinations accounted for fewer than 5% of all cases. When analysing the frequency of complications, reported during early rehabilitation, there was a difference between Münster with 9 patients out of 64 (=14,1%), the main rehabilitation centre of Hannover with 6 patients out of 16 (=37,5%), and other units with one out of 20 patients (=5%).

Posttraumatic epilepsy

EEG recordings at the end of rehabilitation were reported in 159 patients (=62%). Epileptic potentials were diagnosed in six out of these 159 patients (=3,8%). These six patients received an antiepileptic drug medication. No hyperactive electrical activity was recorded in 153 patients (=96,2%); however, 18 of these patients (=11,8%) had an antiepileptic drug prophylaxis.

Rehabilitation therapies (Table 5)

The 206 patients (=80%) were treated on an inpatient status; 180 patients (=70%) were treated in different special working premises for therapy; 130 patients (=50%) were treated on both an in- and outpatient basis. Therapies were normally applied in small groups. However, 16 out of 19 patients suffering

from severe TBI were treated only individually during that time. Daily therapy including weekends was applied in 141 patients (=55%) while 111 patients (=43%) were treated only during working days. Data was not available for six patients. Therapy intensity was independent of TBI severity. Therapeutical measures applied were as follows: physical therapy in 99%, occupational therapy in 87%, activating nursing in 64%, neuropsychological treatment in 59%, speech/language therapy in 45%, neuro-pedagogical service in 34%, vocational/job therapy in 25%, music therapy in 20% and hippo therapy in one patient (=0,4%). The manifold therapies were applied in different combinations at the same state of rehabilitation. Hence 10 out of 19 severe cases of TBI received activating nursing, physical, speech/language, music, occupational, and neuropsychological therapies. Eighty three patients (=72%) out of 115 mild cases of TBI (=44,6% of 258 patients) received the same therapeutic combination of rehabilitative measures.

Table 5. *Therapies performed for rehabilitation treatment on an in-patient basis in 258 patients after acute TBI*

Therapies	Number	[%]
Physio –	256	99.2
Occupational –	224	86.8
Speech/language –	116	45.0
Neuro-pedagogic service	87	33.7
Neuropsychology	151	58.5
Activating sick-nursing	165	64.0
Job –	64	24.8
Free time –	37	14.3
Music –	51	19.8
Hippo –	1	0.4

Table 6. *Early rehabilitation Barthel Index (ERBI) of TBI patients at the beginning of functional neurorehabilitation and at time of discharge*

ERBI at the beginning	N	%	Relative %
−325 to +25	150	58.1	73.5
+26 to 75	29	11.2	14.2
Better +75	25	9.7	12.3
No data	54	20.9	–
Total	258	100	100
ERBI at the end			
−325 to +25	54	20.9	27.7
+26 to 75	33	12.8	16.9
Better +75	105	40.7	53.8
No data	63	24.4	–
death	3	1.2	1.5
Total	258	100	100

Outcome (Tables 6–8)

Mean duration of ENNR (phase "B") was 41 days (1–289 days) as it was for post-acute phase "C" (2–300 days) compared to 80 days (5–841 days) for long-lasting phase "D". At the end of "B" the early outcome was classified into 75 out of 100 patients as GOS 1 in 4% (dead), GOS 2 in 2,2%, GOS 3 in 37,5%, GOS 4 in 26,7%, and GOS 5 in 29% as compared with the outcome of 175 out of 258 patients with TBI at the end

Table 7. *Early functional outcome (GOS) at time of discharge from rehabilitation institute (N = 258 TBI) with regard to GSC assessed at the beginning of TBI rehabilitation*

GOS	GCS at the Beginning				
	Mild	Moderate	Severe	No data	Number
5 no/minimal functional deficits	46 40.0%	8 19.5%	–	15 18.1%	69 26.7%
4 moderate disability	40 34.8%	12 29.3%	3 15.8%	8 9.6%	63 24.3%
3 severe disability	15 13.0%	13 31.7%	10 52.6%	–	38 14.7%
2 vegetative state VS	– –	– –	3 15.8%	– –	3 1.2%
1 dead	–	1 2.4%	1 5.3%	1 1.2%	3 1.2%
missing	14 12.2%	7 17.1%	2 10.5%	59 71.1%	82 31.8%
total number %	115 100.0%	41 100.0%	19 100.0%	83 100.0%	258 100.0%

Table 8. *GCS at the beginning and later social supply in 258 TBI after discharge from rehabilitation*

Social activity at Discharge	TBI severity				
	Mild	Moderate	Severe	No data	Number
home	6 5.2%	3 7.3%	6 31.6%	11 13.3%	26 10.1%
to another hospital	21 18.3%	13 31.7%	7 36.8%	10 12.0%	51 19.8%
home nursing	26 22.6%	8 19.5%	3 15.8%	17 20.5%	54 20.9%
sheltered work	2 1.7%	– –	– –	1 1.2%	3 1.2%
independent self-supporter	50 43.5%	13 31.7%	1 5.3%	37 44.6%	101 39.1%
another social environment	10 8.7%	4 9.8%	2 10.5%	6 7.2%	22 8.5%
missing data	– –	– –	– –	1 1.2%	1 0.4%
all (%)	115 100.0%	41 100.0%	19 100.0%	83 100.0%	258 100.0%

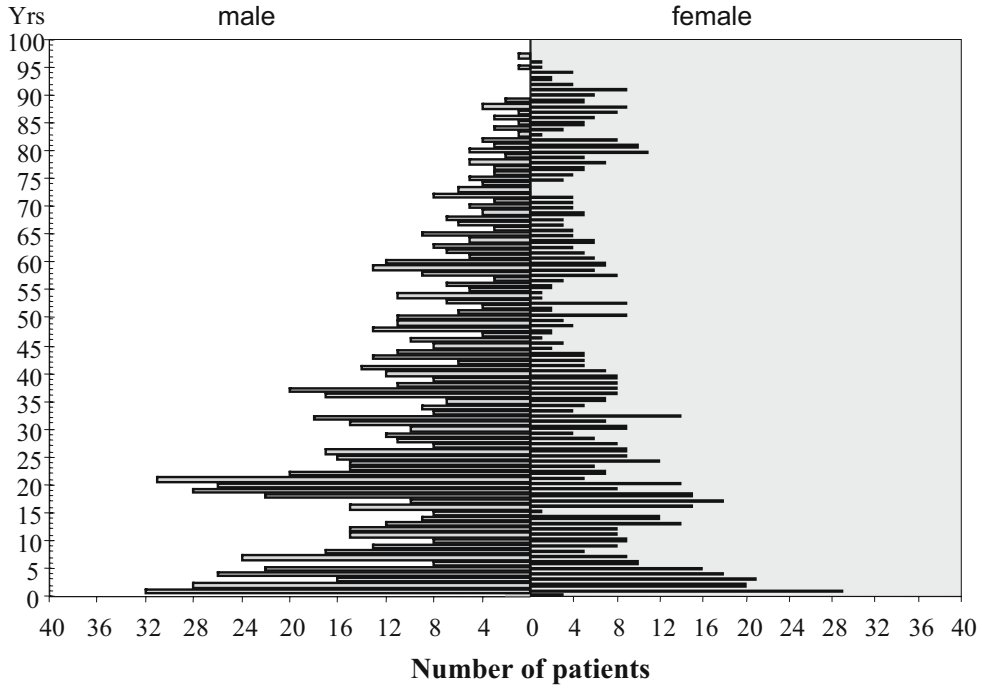

Fig. 1. Age and gender of 6.783 patients after acute TBI

of neurorehabilitation (phases "B,C,D,E") with GOS 1 in 0,82%, GOS 2 in 1,2%; GOS 3 = 14,7%; GOS 4 = 24,3% and GOS 5 = 26,4%. The social outcome after one year follow-up of 4.525 interviewed TBI patients showed in 80% the personal situation unchanged, 8% worsened, 2% severely worsened, with data lacking in 10% of all the patients. Complaints following TBI were reported in 21% of patients. Six victims were still in the rehabilitative process.

On an outpatient basis a total of 363 patients (=5,3% out of all admitted 6.783 TBI) received any kind of neurorehabilitation, but 8,8% when compared to the 4.307 patients that were interviewed after one year. Out of 1.562 patients who primarily had an ambulant emergency analysis 26 (1,7%) patients or 3,1% respectively, out of the 831 interviewed patients were treated on an outpatient basis. They received physiotherapy alone in 2,3%, combined with speech therapy in 0,1%, with vocational therapy 0,1%, with speech and psychological therapy in 0,4%, with vocational and psychological therapy in 0,1%.

Figures from 4.963 primary hospitalised TBI patients showed, with reference to the interview, rehabilitation on outpatient's basis for 241 patients (=7,3% out of 3.299 interviewed TBI.). After hospital discharge 54 patients (=1,3%) of 4.307 interviewed patients received psychological therapy, 1,1% speech, 1,1% vocational, but 7,3% physiotherapy on an outpatient basis.

After one year mortality was 4,7% when 212 patients out of 6.783 TBI were dead. According to the 212 documented deaths, 19 patients (=0,2%) died after hospital admission during initial emergency treatment, 44 TBI (=0,6%) during hospital care, 3 patients (=0,04%) during posttraumatic rehabilitation, six patients because of TBI after discharge, 51 patients because of other reasons, and 89 patients of unknown reasons after their discharge.

Discussion

The prime intention of this study was to analyse reliable data on the resource deployment and the quality of ENNR services in the Münster region described by the senior author, who is a member of the Neurosurgical Clinic, and other early rehabilitation units that have meanwhile been set up nationwide elsewhere. Also epidemiology and quality of acute care following TBI was to be recorded to establish a basis for a planned TBI database in Germany. Since, from a practical viewpoint, such a prospective data-recording project has been considered impossible to be con-

ducted in Germany and other countries, the Study Council decided to select the two major regions of Hannover and Münster due to their sound infrastructure as well as their involvement concerning the observance of the guidelines for acute TBI management and of the German Recommendations for ENNR, published in 1993 [16, 22, 24]. Henceforth these recommendations have been followed by all task-force participants. Three of them are in charge of one of the rehabilitation institutions involved in our study, E.G. in HS in the Hannover area and von Wild K. for the Münster region and Ritz A for children's functional rehabilitation in Bremen Lesum.

According to Hildebrand [5], citation: ''Quality in the hospital [demands] a vision that unites all those involved; measurable targets; the mobilization of the staff; a closely coordinated strategy of action throughout the entire hospital; planning activities oriented towards the targets of the hospital as well as their proper documentation and the dedicated evaluation of the results''. Medical experience, neuropsychological observations, and the numerous scientific papers that have been published over the past decades as a result, have left no room for questioning the necessity and the efficacy of posttraumatic rehabilitation measures for brain-injured patients of all age classes and the need for establishing special wards that are capable of fulfilling these requirements [7, 16, 17, 21, 24].

The decisive factor for the decision to re-include early-rehabilitation beds in the Hospital Requirements Plan of North Rhine-Westphalia and the 20 beds for posttraumatic acute rehabilitation at the Clemenshospital in Münster as a pilot project of the regional state government was the expert opinion that we wrote [7] together with the requirements analysis published by S. Kirchberger [8]. Based on the medical records of acute cases of TBI care of the emergency hospitals in NRW, serving a population of some 17 million people, these authors calculated an annual incidence of 1,900 cases of severe TBI that would need further acute neurorehabilitation (phase B), with 13% of patients > 70 years, $26\% > 60$ years, and 13% in their youth between 11 and 20 years of age. Mortality was 26% within the first ten days of hospitalisation. Ten per cent of all patients with TBI treated in the intensive-care unit were discharged for outpatient treatment after three weeks on the assumption that they had no or only slight impairments. Most of these severe cases of TBI received only acute neurosurgical care and were transferred to another hospital or a different ward of the same hospital after a stay of up to ten days. ''The transfer takes place at a time when rehabilitation efforts should be amplified.'' These authors also observed a type of selection when it came to the allocation of rehabilitation resources. More than one half of patients aged 40 or more, in order to save resources, were ''shunted'' into long-term care without any chance of rehabilitation, while most of the patients aged 20 or under were relatively swiftly given a place in a rehabilitation centre.

This study shows that structural quality and competent management of acute and post-acute TBI treatment including ENNR are now nearly perfect, although posttraumatic rehabilitation institutes have only rarely been asked to admit less than 5% of TBI of different severity.

A system analysis of the pre- and early hospital care in severe head injury in Southern Bavaria (catchment area: 5.86 m) on a population base level, like our study, showed an incidence of 13 per 100.000 population of severe TBI (GCS 8 and less) with falls preferentially affecting patients above 45 years, followed by car- and bicycle accidents [1]. These figures are in accordance with our findings. In comparison with the annual incidence of severe brain trauma in Cologne (1 m inhabitants), incidence was 9,3 per 100.000 population with an overall mortality rate of 46,6%; 60% of deaths occurred within the pre-hospital setting [2]. In the Bavarian area 55% of severe TBI had died on the scene prior to hospital admission. Pre-hospital fatalities were not included in our study. However, we have to take into account that no less than 214 out of 217 Bavarian cases who died prior to hospital admission had sustained severe acute brain lesions as demonstrated at autopsy [1]. The Cologne and Bavarian data will have to be discussed in light of the report published by Murray and the EBIC council in 1999 on incidence, TBI severity, medical treatment, and outcome after 6 months [13]. Of the 847 patients with acute moderate or severe TBI that were considered in this multinational, multicentre study, data of 796 patients (=94%) in the late course were analysed: 31% had died, 51% had a favourable early outcome (moderately disabled, good recovery as per GOS 4 and 5) with a spectrum of variation of 42% for Spain and 68% in France. A conspicuous feature is that when it comes to classifying the severity of TBI-related injuries, it was not possible to distinguish between moderate and severe injuries (GCS 12-9 or 8 and lower, respectively) due to ''*the impossibility to record GCS score in 37%*

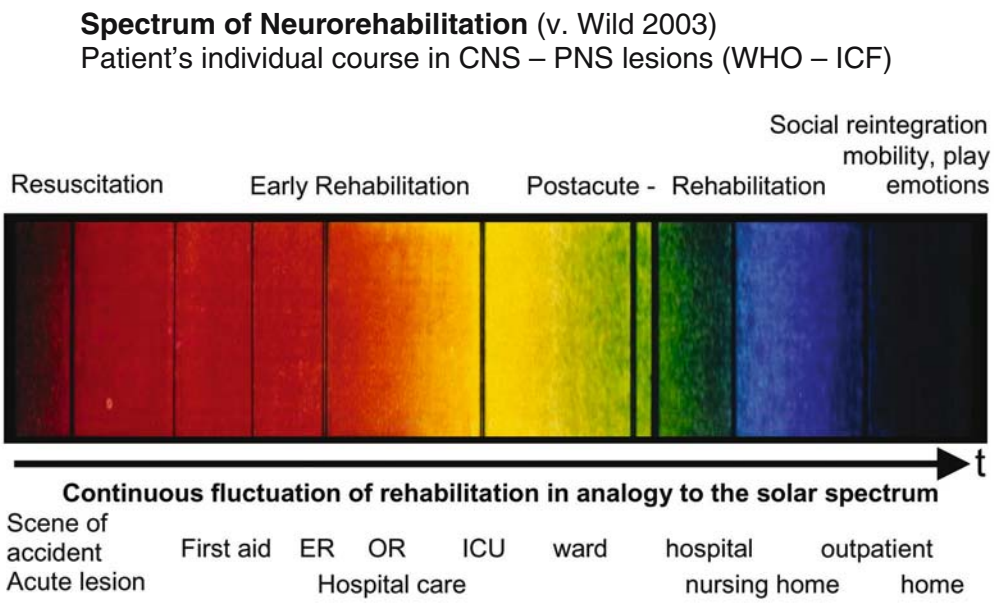

Fig. 2. Spectrum of neurorehabilitation following acute TBI. By analogy to the solar spectrum and its characteristic Frauenhofer lines (black vertical lines), the figure shows the continuous, fluctuating transit of the individual restoration of functions due to holistic multidisciplinary rehabilitation measures over time (*t*), starting with the phase of early rehabilitation and ending with social reintegration of the patient into family, social and vocational life after successful long-term rehabilitation. TBI patients final outcome and health related quality of life depend on the remaining plasticity and rehabilitation potential, the quality of mental-cognitive, neurobehavioral rehabilitation, the point in time and period

of the patients in the respective "neuro" centre", end of citation [13]. In our study, too, classification of the injury severity as per GCS in conformity with the guidelines was possible, roughly, in only one half of all cases during the first six hours after TBI.

Re-evaluation of the documented consciousness, alertness and impairment of subcortical functioning resulted in a reassessment, mainly in the areas of moderate TBI, which is why in our analysis we have taken only the actually recorded GCS data as basis for our calculations (Tables 1–3, 7, 8).

Early rehabilitation

The distinct and interesting differences transpired when the figures of ENNR were compared to general conditions and management, provided on the one hand by the specially designed neurosurgical ENNR unit (phase B) as part of the neurosurgical department in Münster (which is 3 km away from the Medical Faculty Hospital), and the main common hospital for neurological rehabilitation in the Hannover region on the other hand (phase B to D), which is the main neurorehabilitation institute but 70 km distant from Hannover. The time interval between accident and ENNR admission, the nature and severity of TBI, patient's age and duration of stay were significantly different when taking into account the management of secondary complications and secondary admission to other hospitals. All complications could be managed in the same hospital without transferring the patient to another department for medical treatment, except if the patient required internal intensive care or artificial ventilation, the latter being one of the excluding criteria for ENNR admission [16].

The senior author and co-workers retrospectively analysed data of 252 TBI patients who were consecutively treated at the author's specially designed post-traumatic EENR unit as part of the neurosurgical department [6], analysed also in the present study (MS). Among the 252 patients, 68% were classified as having severe, 22% moderate, and 10% mild TBI. These figures differ considerably from those of the present study with 30% severe and 23% mild TBI. Mean duration of intensive-care treatment was 7 days, mean inpatient stay at the ENNR unit was 51 days (range from 4–388 days) which is in accordance with the new data presented here. A number of 134 complications in these 252 patients made it necessary to effect immediate treatment measures. In 27% of cases neurological and

27% single or complex pulmonary complications occurred, in 19% cardiovascular complications, in 18% metabolic and in 9% abdominal complications. A total of 98 secondary neurosurgical interventions were necessary in 71 patients, 23% of whom required additional surgery. In 26% interventions were performed within the first ten days and in a total of 71% during the first month of patient's stay in the ENNR ward. (Outcome GOS) GOS 1 = 6%, GOS 2 = 6%, GOS 3 = 47%, GOS 4 = 24%, and GOS 5 = 18%. The German Coma Remission Scale (CRS) with a 24 point score and measuring cognitive and mental neuropsychological impairment, in addition to the GCS details of the early stage after trauma [16, 22] are now routinely used by all ENNR Task Force members [16, 24]. Regarding prognostic criteria it seems important to note that all patients in the previous retrospective study who had achieved a CRS score of 24 points within 40 days progressed to a favourable early outcome score (GOS 4 u. 5). No patient with a score lower than 20 of a total of 24 points on the CRS on day 40 of ENNR reached a GOS score of 4 or 5, while patients with fewer than 10 points on the CRS score achieved only GOS levels 1 and 2. CRS was also used in our prospective Hannover/Münster study, however such data will be reported elsewhere together with functioning outcome data of FIM, EBRI and patients' social outcome measurement.

The early outcome at the end of neurorehabilitation and after one year was as good as we expected (Tables 6, 7, 8), fully justifying our concept for ENNR as well as the enormous costs involved [16, 18, 22, 24]. Analysis of the TBI age groups with regard to initial TBI severity and to GCS at the time of discharge from acute hospital care showed no more significant differences than those previously observed. This is in accordance with our previous findings that during rehabilitation elderly patients will finally recover to a similar extent as the younger population, although it may take longer before they can be dismissed home to stay on their own.

The relatively high percentage of patients with mild forms of TBI admitted for institutional rehabilitation underline the importance of neurorehabilitation for this group who are usually sent home [10, 19, 23]. This is also shown in our study for those patients with mild TBI who were initially sent home without any treatment or special recommendations for out-patient neuropsychological rehabilitation. So far neurobehavioral cognitive posttraumatic disturbances of mild TBI has usually been underestimated, in spite of the known fact that impaired higher nervous functions remain responsible for the major disabilities following TBI.

Regarding management and outcome of TBI as part of polytrauma previous studies by E. Ortega-Suhrkamp [15] clearly demonstrated that the functional outcome as measured by FIM, FRBI, and GOS was significantly the same in isolated TBI as in TBI patients suffering from polytrauma, except that polytraumatized TBI required a substantially longer rehabilitation phase, i.e. 102 days versus 78 days. Kawasny and co-workers [11] analysed 225 consecutively treated, polytraumatized patients at the trauma centre Vienna. Limbs were most often affected in 80%, followed by thoracic lesions in 74%, TBI in 71%, lesions of the abdomen in 34%, pelvic region in 32% and spine in 19% of the victims. These figures are in accordance with the previously reported data from the accident-emergency department of Medical University Hannover (MHH), which participated in our study.

Conclusions

Occurrence of TBI in the two regions as analysed 15 years ago differs from the data today. Falls are the major cause of TBI, especially in the elderly population, instead of traffic accidents, a fact that must be duly considered in view of prevention in the future. At that time only 5% of patients with TBI were given neurorehabilitation despite the established diagnosis of impaired higher nervous functions at the time of hospital discharge. These victims belonged to all age groups and presented all kinds of TBI severity. When early neurological-neurosurgical rehabilitation (ENNR) was introduced in accordance with the standards as formulated by the German ENNR Task Force (16) – which can be seen in our study – functional results were as anticipated. Special units for posttraumatic neurosurgical rehabilitation, such as the one designed in Münster by the senior author as a pilot project of the NRW government in 1993, have soon demonstrated superiority of early posttraumatic TBI rehabilitation. Results have been as efficient and effective as previously predicted. Neuropsychological rehabilitation from the beginning is of utmost importance to help restoration of impaired higher nervous functions in TBI patients [17]. This issue was also analysed but will be presented separately reporting on patients' outcome and health related quality of life after head trauma (see contribution Nicole von Stein-

büchel this vol. pp. 43). Rescue, first aid, acute medical hospital treatment, and functional posttraumatic neurorehabilitation are in accordance with national and international guidelines used locally and routinely as well as recommendations based on expert opinion. Thus high standard quality management following TBI could be guaranteed in our 6800 patients within the first year of treatment and early rehabilitation in the Hannover and Münster regions. The collected data might be used for a TBI data base in Germany being on the way.

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Posttraumatic epilepsy with special emphasis on prophylaxis and prevention

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Summary

Posttraumatic epileptic seizures have an incidence of about 10% in series of severe head injuries. Control of ''early seizures'', i.e. those occurring in the first week after injury, is mandatory. Attacks, especially if recurrent, may add secondary damage to the injured brain: intravenous phenythoin with therapeutic plasma level allows control of the attacks. Seizures occurring months or years after injury are called ''late seizures'': recurring ''late seizures'' make up the clinical syndrome of ''posttraumatic epilepsy''. ''Prophylaxis'' should mean that drug treatment, given for a more or less prolonged period of time, blocks permanently the ripening of the epileptogenic foci avoiding the occurrence of seizures. In animal ''prophylaxis'' by antiepileptic drugs seems efficacious in many experimental models including iron induced epilepsy which is considered a model of posttraumatic epilepsy and vice versa. In the human being ''prophylaxis'' has been attempted with: phenytoin, phenobarbital, carbamazepine, valproate but without success. During treatment period the occurrence of seizures is prevented but, after discontinuation of the drug, seizures occur just as in non treated patients. The ripening of the epileptic focus in posttraumatic epilepsy, as in iron induced epilepsy, seems to be due to a cascade of events beginning with haemorrhage, haemolysis, iron or heme compound liberation, free radical formation, peroxidation and cell death. Experimentally free radical scavengers and antiperoxidants have marked prophylactic effect. Some of them (phosphate diester of vitamin E and C, melatonin, vanillyl alcohol) may be employed in clinical practice, but up to date there is no controlled study in human beings.

Keywords: Posttraumatic epilepsy; prophylaxis; prevention; free radical scavengers; antiperoxidants; antiepileptic drugs.

Introduction and definition

Posttraumatic epilepsy is a disorder characterized by recurrent seizures, not referable to another obvious cause, in patients following traumatic brain injury.

Seizures may occur within a few hours after injury, ''immediate seizures'' [25], [common in children [35]] and within the first week after injury, ''early seizures'' [13, 26, 27]. Incidence, characteristics, relationship between age, severity of trauma and ''early seizures'' have been thoroughly analysed by Pagni [35]. Incidence of ''early epilepsy'' in severe head injuries is 6–10%: 90 out 1091 cases, 8.2%, in the series of De Santis and Pagni [10]; in trivial injuries about 3%: 73/2170, 3.3% [10]; in operated intracranial posttraumatic lesions about 19%: 25/127, 19.6% [10].

Seizures occurring weeks, months or years after injury are termed ''late seizures'' and only recurring ''late seizures'' make up the clinical syndrome which can be labelled as ''posttraumatic epilepsy''.

For a long time ''early seizures'' were considered of no relevance as far as ''late epilepsy'' is concerned. But ''late epilepsy'' is significantly more common in patients who have suffered from ''early fits''. Broadly speaking 17–33% of patients with ''early seizures'' will present ''late seizures'' in front of only 2–5% of patients without ''early seizures'' (see 13, 35).

Overall incidence of posttraumatic epilepsy in different series of consecutive, unselected trivial and sever injuries, including mainly closed head injuries, is about 3–5%. If a large number of open head injuries is included the incidence rises to 8–9% [28, 35]. Higher values have been occasionally reported (see 18): that is mainly due to different criteria of recruitment of the patients: inclusion or exclusion of cases with a single fit or only of cases with repeated attacks; various length of follow-up; neurosurgical series versus series including mainly outpatients; inclusion of high number of open juries etc.

Incidence of posttraumatic epilepsy varies widely according to the type of injury and efforts were made to identify risk factors. In series of non-missile combat injuries the incidence reaches the value of 12–24%; in penetrating missile combat injuries the incidence is 34–53% [35, 40, 45, 47]. In non-missile civilian intracranial surgical traumatic lesions the incidence reaches 20–33% [10, 35, 36].

On the basis of the analysis of the pathological characteristics of injury, clinical picture, CT scan data, the following were identified as the most relevant risk factors that increase the incidence of posttraumatic epilepsy: penetrating missile injury/incidence of late seizures 53%; intracerebral haematoma-laceration 39%; focal brain damage on early CT scan 32%; early seizures 25%; depressed fracture-torn dura 25%; extradural or subdural haemorrhage 20%; focal signs (hemiplegia, aphasia) 20%; depressed skull fracture 15%; loss of consciousness >24 hours 5%; linear fracture 5%; mild concussion 1% [11, 28, 40, 45, 47]. Introduction of the CT scan provided better assessment of these factors. Duration of unconsciousness or coma is not *per se* a relevant risk factor provided cerebral contusion and/or laceration are/is absent. Not a single patient in coma with normal CT scan, i.e. no evidence of diffuse brain injury or brain swelling, thus without focal brain damage, presented with late seizures at a mean follow-up of 4,1 year [12]. Focal brain damage on an early CT scan after injury significantly increases the risk of posttraumatic epilepsy [7]. In a personal series of 280 patients operated on for intracranial lesions, followed up for 1–9 years, (treated for at least 1 year with phenobarbital 50 + 100 mg/day) late seizures occurred in 48 out 280 cases (18%). Incidence was very low in cases of pure extradural haematoma and higher in cases with brain haemorrhagic contusion and/or laceration. Pure acute subdural haematoma: cases 41, seizures occurred in 5 = 12%; acute subdural haematoma + contusion/laceration: 73/8 = 11%; depressed fracture + contusion/laceration: 55/15 = 27%; pure extradural haematoma: 21/1 = 4%; extradural haematoma + contusion/laceration: 34/8 = 23%; laceration: 56/11 = 19%; total 280/48 = 18% (see also 36).

Over 50% of late seizures occur within one year since injury, 70–80% within two years. Thereafter for about ten years 3–5% new seizures occur yearly. Thus in over 15% of patients the first attack may occur more than 5 years after injury, and another 5% will not manifest epilepsy until 10 or more years later. Cases have been reported of epilepsy developing 20 years since trauma (see 35).

In all the reported series [6, 28, 47] generalized seizures account for 30–40% of the attacks; focal attacks becoming secondarily generalized for another 30–40%; partial seizures with elementary symptoms for 10–20% and partial complex seizures for another 10–20%.

Recurrent posttraumatic seizures may exert an adverse impact upon the cognitive performance, activity and life style of patients depending on the number of seizures. Attack frequency varies widely: from but a single seizure to a few attacks a year; sometime the attack number is very high and defies an accurate count [5, 35]. The attack frequency does not usually change during the life. In this connection it is worth-while to note that in retrospective studies on aetiology of epilepsy (which in about a half of the cases is unknown), birth injury accounts for about 20% of the cases, and a head injury sustained after birth in 10–12% of the overall epileptic population [2, 17].

Thus posttraumatic epilepsy may appear, sometime, as a benign disease, but in at least one third of the cases it is a severe burden for the patient [4]. Therefore many attempts to prevent posttraumatic epilepsy have been reported in the literature since more than half of a century.

Pathogenesis of posttraumatic epilepsy

Blood in contact with cerebral cortex, as in brain contusion/laceration, seems to be the triggering factor of the epileptogenic process in the human [28, 47], just as intra-cortical injection of blood, heme compounds and $FeCl_2$-$FeCl_3$ produces, in animals, chronic epileptogenic foci, which have pathologic features and electrophysiological pattern of discharge similar to that of human epileptic foci [43], and provoke recurrent seizures in animals [19, 24, 52, 54]. Thus the iron-induced epilepsy may be considered a model of posttraumatic epilepsy and vice versa. The mechanism of epileptic focus formation might be the following. Iron or heme compounds give rise to a cascade which through free-radicals initiate and propagate lipid peroxidation. Lipid peroxidation eventually causes disruption of membranes of subcellular organelles and degradation of deoxyribose and aminoacids, and inhibition of Na-K ATPase (see 52, 53, 54). This process causes cellular loss with reparative gliosis and subtle alteration in neuronal plasma membranes which could lead to a progressive depolarisation. The synchronisation of a critical mass of neurons becomes sufficient to cause clinical manifestations [42]. Thus the process might be blocked by drugs preventing free radical formation and inhibiting lipid peroxydation: tocopherol, tocopherol + selenium [52]; cholesterol, proteins and sulphydril group of glutathione [1]; vanillyl alcohol [22]; melatonin [23]; phosphate diester of vitamin E

and C [32, 57]; adenosine, chloroadenosine [58] and, last but not least, phenobarbital [8].

Prophylaxis of posttraumatic epilepsy and prevention of the attacks

Experimental researches demonstrate that, in animals, epilepsy due to intracortical injection of blood may be prevented by phenytoin, phenobarbital, carbamazepine and valproic acid, but on condition that drug administration begins immediately after the application of the epileptogenic agent. Such a drug administration, even for short period of time, seems to block the ''ripening'' of the epileptogenic focus, avoiding permanently the occurrence of seizures. This was demonstrated not only in rabbits and cats but also in genetically-seizure-predisposed primates (see 20).

But ''prophylaxis'' and ''prevention'' of posttraumatic seizures in the human is still one of the most debated problem. Prophylactic treatment is any therapeutic ''measure taken to prevent disease in an individual ...'' (see Dictionary of Medicine and Biology). In posttraumatic epilepsy ''prophylaxis'' should represent a treatment, administered for a more or less prolonged period of time, which blocks the ''ripening'' of the epileptogenic foci giving rise to the attacks, thus avoiding permanently the occurrence of seizures.

''Prevention'' means simply to hinder the occurrence of the attacks without any attempt to block the pathogenetic mechanism, that is without hampering the development of the epileptogenic focus. To evaluate the efficacy of prevention it is of course sufficient to control the number of seizures, if any, in patients to whom antiepileptic drugs in the therapeutic range are given and the number of patients presenting, or not presenting, attacks during drug administration. To evaluate the prophylactic effect of treatment it is compulsory to collect series with a long term follow-up after discontinuation of treatment to verify if seizures occur. In fact late seizures may occur years after injury.

In posttraumatic epilepsy the term ''prophylaxis'' has been incorrectly referred to anticonvulsant treatment administered to patients who have not yet developed manifested seizures (see 56). Moreover, the evaluation of the ''prophylactic'' effect has usually been limited to the period of administration of the drugs, and information on the occurrence of seizures after the discontinuation of the treatment has not been reported: consequently in these instances only ''prevention'' of seizures has been evaluated.

First of all we must ask ourselves if there is any justification for ''prophylaxis'' and ''prevention'' in posttraumatic epilepsy. No doubt ''prevention'' of ''early seizures'' is mandatory in the 7–15 days after injury. In fact partial (especially if recurrent) and generalized attacks may add to a secondary damage to the injured brain, for instance by increasing intracranial pressure, hypoxia etc. [9]. Prevention and prophylaxis of ''late seizures'' could help the patients to avoid further accidental injuries, cognitive impairment, loss of driving licence or employment etc..

Prevention of early seizures

As far as the ''prevention'' of early seizures is concerned, the attitude and ideas changed in the last 30 years. When phenytoin was administered only by oral or intramuscular route the studies of therapeutic serum levels indicated a time lapse of up to 1–2 weeks before an effective level could be achieved (see 44). The same holds true for phenobarbital. Thus there were no data supporting the use of prophylactic phenytoin for early seizures control. However, the results changed since intravenous phenytoin became available.

In a double blind controlled study Young *et al.* [60] reported that patients receiving phenytoin had the same number of early seizures than the placebo group and concluded that phenytoin alone, in the *generally accepted therapeutic doses*, has no prophylactic effect. The authors report that patients were administered phenytoin intravenously or intramuscularly and that they ''obtained plasma concentrations above 10 μg/ml in 82.9% of the patients by 24 hours after administration of the drug. At 72 hours, 84.6% of patients, and at the end of the week 78.7%, had therapeutic plasma concentration of phenytoin'', that is 10–20 μg/ml. At the time of the seizures two patients had plasma level of phenytoin lower than 10 μg/ml (that is into the subtherapeutic range); one between 10–12 μg/ml; and two over 12 μg/ml. Summing up, the lack of control of seizures seemed to result from the low serum level of phenytoin. Therefore Young *et al.* [60] recommend phenytoin plasma concentrations of 25 to 30 μg/ml as necessary to control early seizure and suggest that loading doses should be calculated to provide immediately high phenytoin blood levels, adding phenobarbital if phenytoin does not provide seizures control.

Glotzner [15] maintained carbamazepine was effective in controlling early seizures: but, because also phenobarbital was administered to 61% of the patients

and diazepam to 59% "in the acute posttraumatic period for sedation", we wonder if the control of the attacks should not be referred to those drugs.

Temkin *et al.* [51] in a controlled study observed that early seizure rates were lower in patients treated with an intravenous loading of phenytoin to reach and maintain a plasma level in the range of 10–20 μg/ml. The same was observed in patients treated with valproate.

Other reported that control of early seizure may be achieved by the use of phenytoin, if the initial dose of medication (up to 20 mg per kilogram) is given intravenously and serum phenytoin levels controlled in the following days: Temkin *et al.* [50], Pechadre *et al.* [38], Temkin *et al.* [51] observed an incidence of 1.5–6% of early seizures in treated groups against a 14–24% occurrence of seizures in placebo treated groups. In Wohns and Wyler [55] series none of the treated patients had seizures in the first week.

On the basis of these reports control of early seizures with intravenous phenytoin has been recommended: because "this technique has been very successful in preventing seizures after attaining adequate therapeutic blood level". It has become a routine treatment and to day it is widely employed in severe head injury (see: Guidelines for the management of severe head injury. The brain trauma foundation 1998). However there is no evidence that control of early seizures improves outcome in severe brain injuries.

Propylaxis and prevention of late seizures

Surgery

The first attempt has long since been a surgical one: the objective was to prevent or to minimize the meningo-cerebral scarring (which seems to be a discharging lesion) by meticulous removal of contused and necrotic brain slabs, by leaving adequate vascular supply to the surrounding intact gyri, by removal of blood clots, meticulous haemostasis and by plastic reconstruction of the torn dura. The expectation was to reduce the incidence of posttraumatic epilepsy. Unfortunately, as we now know, this has not been the case (see 5). And, strange enough, retained bone fragments in penetrating injuries, a use of dural graft, cranioplasty and not even brain abscess or family history of epilepsy seem to have any impact on the incidence of late epilepsy [47, 49]. There is no information on the possible influence, on the incidence of late epilepsy, of the interval between injury and operation in cases of depressed skull fracture, brain laceration, haematoma, open trauma and penetrating injury.

Drugs

Antiepileptic drugs

Reports in the literature have shown many attempts towards prevention and prophylaxis of the posttraumatic epilepsy by drugs. But to reach definitive conclusions is a difficult task. Usually, the studies devoted to the problem are unsatisfactory for many reasons: limitation in test design or in population size inhibits adequate statistical evaluation; adequate follow-up of the whole population is usually impossible: many patients are lost; control of the drug compliance is often impossible; control of adequate drug plasma level is difficult and in many studies not employed; the immediate start of the therapy after injury was often impossible; specific information regarding injury severity, duration and method of follow-up are sometimes not reported; in most of the presented studies there was no long-range follow-up after drug withdrawal so that the evaluation of the "prophylactic" efficacy of the treatment was impossible. Moreover many studies were retrospective, uncontrolled or not randomised.

The reports on the efficacy of anticonvulsants in preventing seizures during the period of drug administration are often contradictory, where "prophylaxis" is confounded simply with a "prevention" of the attacks [37].

In some series of severe injury (surgical series, cerebral laceration, torn dura) treated with phenobarbital, phenytoin or both, incidence of seizures is nil [48] or very low, 2–5.6%, that is inferior to the incidence which could be anticipated [36, 37]. In controlled series the incidence of seizures is much lower in the treated group than in the groups of non treated patients: 2 out 48 treated cases, that is 4%, versus 17 out 46 not treated cases that is 36%, in the series of Hoff and Hoff [21] and Birkmayer [3].

On the contrary Caveness *et al.* [5], Young *et al.* [60], Glotzner [15], Temkin *et al.* [50] state that anticonvulsant therapy by phenytoin and carbamazepine does not "prevent" the occurrence of posttraumatic seizures during drug administration. In the series of Temkin *et al.* [50], during one year of treatment by phenytoin, seizures were more frequent in the treated

than in the placebo group! Probably many patients, in one study [59], received subtherapeutic doses of the drug. In other studies the period of treatment was very short up to 3–6 months only [20]. As far as our opinion is concerned during the period of treatment phenobarbital and phenytoin are very efficient in controlling late seizures [36].

The problem of "prophylaxis" seems to be more complex.

There is a group of uncontrolled studies [33, 34, 37, 55, 59] and some randomised study [14, 38] which suggest that anticonvulsant treatment might be useful in prophylaxis of posttraumatic seizures (see also 30).

The first relevant study on record is by the Czechoslovakian. Initiated in 1963 it was published in 1969, 1981 and again in 1991 [34, 41, 48]. Patients (75% closed injury with brain contusion, 12.5% basal skull fracture, 10% penetrating injuries) were treated with phenytoin 160–240 mg/day and phenobarbital 30–60 mg/day for at least two years. After two years the medication was discontinued over a period of 6 months. Reported results are astonishing. In fact no patient presented seizures during treatment; after withdrawal of treatment, during 6–13 years follow-up, seizures occurred only in 3 out 143 (2.1%) of the patients. But the most extraordinary results are those referred by Gabor [14]. No patient treated for two years with phenobarbital 30 mg/day and phenytoin 200 mg/day had seizures at 32 months follow-up after treatment interruption. In the opinion of the Czechoslovakian (the group of 143) "the effectiveness of pharmacological prophylaxis of posttraumatic epilepsy was proved in patients with severe brain injury".

These studies are of interest for the fact that treatment seems to have created a true "prophylactic" effect and appears to have blocked the development of epileptogenic foci.

But Penry *et al.* [39] are of the opposite view. Unfortunately their study was not published in extenso. In this well planned, double blind, randomised, controlled prospective study (started within 12 hours from injury), the treated group received phenytoin 200 mg/day and phenobarbital 60 mg/day for 18 months. In a 3–6 years follow-up 85 out of 103 patients remained seizure free but 18, that is 17%, developed epilepsy. They state there was no significant difference in incidence of seizures between the treated and the placebo group. But it seems attack occurred in 23% of the treated group and in 13% of the placebo protocol!

Successful results seem to have been obtained with phenytoin in controlled studies. Wohns and Wyler [55] and Pechadre *et al.* [38] reported a significant lower incidence of seizures in treated patients versus not treated patients also after interruption of drug administration. In the study of Whons et Wyler [55] concerning high risk patients, treatment begun within 24 hours of the injury, with a 1-gm intravenous loading dose and then continued during a year with 400 mg/day to provide serum levels within the therapeutic range of 10 to 20 μg/ml; after treatment interruption the patients were followed up for 4 years; incidence of seizures was 5 out 50, 10% in the treated group versus 6 out 12, 50% in the non treated group. In the series of Pechadre *et al.* [38] (intravenous hydantoin administration was started immediately after injury, and then continued orally for 3 months to 1 year) the follow-up was limited to 1 year after drug discontinuation. Therefore it appears that prophylaxis for three months is sufficient to block the ripening of the epileptogenic foci. Perhaps the critical point is the beginning of treatment which should be immediate or in the first 24 hours after injury.

Mc Queen *et al.* [31], Temkin *et al.* [50], Salazar [46] reached the opposite conclusion: phenythoin at therapeutic or near therapeutic level has no prophylactic effect on late seizures. Salazar [46] followed-up a population of 468 war penetrating head injury for about 15 years. Most of those patients were loaded with intramuscular (Vietnam War!) and then switched to oral phenytoin as soon as practicable. The majority (90%) received "standard doses of phenytoin" (other informations are lacking) and 80% (that is about 350) were still receiving continuous phenytoin at the end of one year. The group of patients who received phenytoin was compared to another smaller group (number of cases is not reported) who did not. The incidence of epilepsy in the two groups was not significantly different either at 5 or at 15 years follow-up: 51% of the ones who received phenytoin versus 32% of those who did not. The inconclusive results may be the consequence of the fact in this series obviously it was impossible to reach a phenytoin therapeutic plasma level in the first 24 hours after injury. The conclusions of Salazar [46] have a strong support from the report of Temkin *et al.* [50] in which the same conclusion was reached as far as "prophylaxis" of late seizures is concerned, because this study [50], patients being loaded with the drug within 24 hours since injury, provided convincing evidence of the effectiveness of phenytoin in preventing seizures during the first week after injury!

Murri *et al.* [33] claim a prophylactic effect of Phenobarbital. But unfortunately in this study the follow-up period after drug discontinuation was short and limited to 1 year.

Glotzner *et al.* [15, 16] attempted prophylaxis by carbamazepine. In the first paper [16] they maintained carbamazepine had a prophylacitc effect on late seizures; but the conclusion of the second one [15] is that carbamazepine is efficacious for control of early seizures, but has no prophylactic effect on late seizures.

A major criticism referred at those studies is that in many the therapeutic serum level of the drugs was not controlled. Dosages considered sufficient to produce therapeutic drug levels have been usually employed but owing to the reported difficulty in controlling the compliance of patients many patients had probably sub-therapeutic levels of the drug.

There is, therefore certainly a difference between prevention and prophylaxis. No doubt prevention, that is control of occurrence of attacks during treatment, is efficacious. In my series of 424 surgical cases, with risk factor of late epilepsy of 15–39%, only 24 patients, that is 6%, presented with seizures during treatment [36]. Moreover other reports clearly demonstrate that in severe head injury, with high risk of occurrence of seizures, the anticonvulsant treatment with Phenytoin, Phenobarbital, Carbamazepine reduces significantly the incidence of the attacks during treatment.

As far as prophylaxis is concerned we can confidently affirm that in spite of the reports claiming that prophylaxis of post-traumatic epilepsy is efficacious, the problem is far from being solved and some data are against the efficacy of prophylaxis by anticonvulsant drugs usually employed.

There is a common observation contrary to a "true prophylactic effect" of anticonvulsant medication. Many patients do not present seizures during the more or less long periods of anticonvulsant treatment. But after the interruption of the medication they present with seizures. This is a very common experience reported everywhere in the literature. The same observation claims the senior author (C.A.P.) with many hundred children followed up for many years after injury, to whom anticonvulsant treatment was given even to control parents' anxiety. It is another proof that so called prophylactic treatment does not always block the ripening of the epileptic focus but simply suppresses attacks [20, 31, 33, 37, 55]. The experimental research suggests that prophylaxis, producing the desired effect, must begin immediately after trauma. Thus the question arises: how many patients really reach an adequate drug plasma level immediately after injury? We suspect further controlled studies are necessary.

Therefore we must ask ourselves, should the treatment start in all the cases and continued for several years? In our opinion, in blunt head injuries with low risk of occurrence of epilepsy it is perhaps better to wait, the treatment should begin only after the first seizure occurred. In high risk patients and after surgery we suggest to start treatment early and to continue with it for a long time, with careful control of its side effects.

Other drugs

If ripening of post-traumatic epileptogenic foci is the consequence of the cascade of events beginning with intracortical haemorrhage, haemolysis, iron or heme compounds liberation, free radicals formation, with final consequence of lipid peroxidation up to the cell death, the ideal pharmacological prophylaxis should include drugs blocking or counteracting any step of the cascade, allowing an enduring block of the epileptogenic process. Provided the cascade begins immediately after injury, treatment should start as soon as possible after injury.

Some antiperoxidants have been tested against iron epilepsy in experimental trials.

Willmore [52] observed that tocopherol pre-treatment, along with selenium, prevents both peroxidation and epilepsy due to iron injection into the rat hippocampus. This treatment prevented also iron-induced histopathological changes. Bicucullin-induced epilepsy (not associated with peroxidation) was not prevented by tocopherol pre-treatment.

Salazar [46] stated intravenous administration of superoxide dismutase in animals blocks the ripening of epileptic foci.

The possibility that phenobarbital might be effective as prophylactic treatment, perhaps in association with other drugs, must be also born in mind: Demopoulos *et al.* [8] observed antioxidants effects of barbiturates in model membranes undergoing free radical damage. That could explain the very low rate of seizures in the series of Pagni *et al.* [36], in spite of the fact they treated high risk patients, with a risk of late seizures of at least 15–39%.

Recently it has been demonstrated that the phos-

phate diester of vitamin E and C (EPC), a potent hydroxy radical scavenger prevents the occurrence of epileptic foci and seizures induced by intracortical injection of iron ions in rat [32, 57]. Yamamoto *et al.* [57] suggested it can be useful in clinical practice.

Similar results, in the same experimental model, have been observed by Yokoi *et al.* [58] with adenosine and 2-chloroadenosine, and by Hsieh *et al.* [22] with the Vanillyl alcohol, a free radical scavenger which inhibits lipid peroxidation. Vanillyl alcohol being a component of Gastrodia eleata Bl. , which is a herb of the traditional Chinese medicine widely employed to treat convulsive disorders or dizziness!

Lastly melatonin, which exerts hydroxyl radical scavenging properties and inhibits lipid peroxidation, has been demonstrated to inhibit iron induced epileptic discharges in rat [23], and seizures induced by kainic acid, by potassium cyanide and by L-cysteine in mice [57].

In all those papers the preventive antiepileptic effect was more marked if drugs were administered before the injection of the epileptogenic agent.

What is worth noting is that phosphate diester of vitamin E and C, vanillyl alcohol and melatonin may be employed in clinical practice.

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Swallowing therapy – a prospective study on patients with neurogenic dysphagia due to unilateral paresis of the vagal nerve, Avellis' syndrome, Wallenberg's syndrome, posterior fossa tumours and cerebellar hemorrhage

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Summary

Background. No studies exist dealing with the outcome of dysphagic patients with posterior fossa (IV. ventricle) tumours (PFT) or cerebellar hemorrhage (CH), and the outcome of patients with Wallenberg's syndrome (WS) after functional swallowing therapy (FST) has so far not been studied in detail.

Patients and methods. 208 patients with neurogenic dysphagia (ND) who were consecutively admitted for functional swallowing therapy (FST) over a 3 year period to our hospital were examined clinically, by use of a videofluoroscopic swallowing study (VFSS) and/or fibreoptic evaluation of swallowing (FEES). The most frequent etiology was stroke (48%), followed by CNS tumours (13%). In the present study we defined three groups. Group 1 comprised 8 patients with PFT or CH. Group 2 consisted of 27 patients with WS, which was the leading cause among patients with non-hemispheric stroke. Since in WS a vagal nerve paresis due to affection of the Nucleus ambiguus occurs, 8 patients with Avellis' syndrome or unilateral paresis of the vagal nerve served as controls and were defined as group 3.

Findings. In the three groups, functional feeding status showed significant improvement after FST comprising methods of restitution, compensation and adaptation, each of which were applied in more than 80% of patients. Outcome was, however, significantly worse in group 1 as compared to group 2 and in group 2 as compared to group 3. Dysfunction of the upper esophageal sphincter and reflex triggering were significantly more severely disturbed in groups 1 and 2 as compared to group 3. Group 1 showed significantly more severe disturbances of the oral phase as compared to groups 2 and 3. After FST, more than 50% (5/8) of group 1 and 30% (8/27) of WS patients (group 2) were dependent on tube feeding, whereas all patients of group 3 were full-oral feeders.

Interpretation. This is the first study dealing with the outcome of dysphagic patients with PFT or CH. Based on our results it can be assumed that in these patients pressure is exerted on both dorsomedial central pattern generators (DMCPGs) for swallowing in a posterior-anterior direction. Due to the importance of the DMCPGs for swallowing, bilateral (and often MRI-invisible) lesions seem to be very harmful. For a better understanding of the pathomechanism responsible for ND in patients with PFT or CH, modern imaging methods such as proton magnetic resonance spectroscopy should be used for studying metabolic changes in the dorsal medulla in the future. Since the outcome of patients with WS with regard to dependence of tube feeding was not associated with the site or size of the lesion, it may – due to the individual asymmetry of the swallowing-dominant forebrain hemisphere – depend on the side of the medullary infarction.

Keywords: Dysphagia; outcome; Wallenberg's syndrome; posterior fossa tumour; cerebellar hemorrhage; Avellis' syndrome; central pattern generators for swallowing.

Introduction

Recently, we published the results of a prospective study on 208 patients with neurogenic dysphagia (ND) who were admitted to our hospital over a 3-year period for functional swallowing therapy (FST) [11]. The two most frequent etiologies in this population were stroke (48%) and brain tumours (13%). Whereas many studies exist which deal with hemisperic stroke and ND [3], ND has not been fully understood in patients with Wallenberg's syndrome (WS) and in those with posterior fossa (IV. ventricle) tumours (PFT). This is reflected by the fact that reports on the frequency of ND in WS vary in the literature between 51% and 100% [12] and that no study exists which deals with the association of ND and PFT. Since in WS, a vagal nerve paresis due to affection of the Nucleus ambiguus occurs, we chose patients with vagal nerve paresis due to Avellis' syndrome (AS) or unilateral peripheral paresis of the vagal nerve (PVN) as controls. In the presence of PFT, pressure is exerted to the brainstem in a posterior-anterior direction. Therefore, we also included patients with cerebellar hemorrhages (CH) because of a similar pathomechanism. In this article, we report on dysphagic patients with these etiologies.

Table 1. *Sample characteristics of the three patient groups and statistically significant differences within or between the groups after FST. Mean or median, range and standard deviation (SD) are shown (for abbreviations: see text); >denotes significantly better*

Patient groups	Age (mean, range, SD) years	Sex M : W	Duration of disease (median, range, SD) days	Duration of FST (median, range, SD) days	Number of patients dependent on tube feeding (TF) or tracheal cannula (TC)	FFS (comparison before and after FST)
Group 1 (n = 8)	57.9	3 : 5	54	72.5	Admission:	
– Posterior fossa tumours (n = 5)	(47–65)		(12–540)	(28–203)	TF: 8/8	
ependymoma °II (3)	7.1		182.2	70.6	TC: 7/8	
meningioma °I (1)						>
haemangioblastoma °1(1)					Discharge:	
– Cerebellar hemorrhage (n = 3)					TF: 5/8	
					TC: 4/8	
Group 2 (n = 27)	65.6	22 : 5	42	70	Admission:	
– Wallenberg's syndrome	(52–86)		(7–3500)	(4–210)	TF: 27/27	>
	9.9		679.5	51.6	Discharge:	
					TF: 8/27	
Group 3 (n = 8)	53.6	6 : 2	18.0	36.5	Admission:	
– Avellis' syndrome (n = 3)	(24–83)		(10–433)	(13–59)	TF: 5/8	
– Unilateral PVN (n = 5)	18.4		145.9	49	Discharge:	>
carotid endarterectomy (4)					TF: 0/8	
vagal neurinoma (1)						

Significant differences between groups after FST (combination of methods of restitution, compensation and adaptation in 80% of all patients): *FFS* group 3 > group 2; group 2 > group 1; *Disturbed reflex triggering* group 3 > groups 1, 2; *UES dysfunction* group 3 > groups 1, 2; *Oral phase problems* groups 2, 3 > group 1.

Patients and methods

For assessing the degree of ND on the activitation limitation level, as defined by the ICF of the WHO [18], we used an ordinal scale reflecting the functional feeding status as target variable (FFS) which was developed by us for this purpose [11]. VFSS and FFS evaluation before and after swallowing therapy were performed following standard protocols [5, 13]. The degree of penetration/aspiration was measured by use of 4-point ordinal scales developed by Schröter-Morasch [13] for FEES (from 1 = occasional aspiration, normal cough reflex to 4 = permanent aspiration, absent cough reflex, no sufficient volitional effort to eject) and by Hannig [5] for VFSS (from 1 = penetration to 4 = aspiration of >10% of the bolus volume and absent cough reflex). For the evaluation of a delayed swallowing reflex and amount of dysfunction of the upper esophageal sphincter (UES) we used the VFSS results (0 = normal, 1 = delayed/disturbed, 2 = severely disturbed/delayed/absent). Retentions in the valleculae and/or piriform sinuses were evaluated with regard to their side (unilateral, bilateral) and amount (0 = no retentions; 1 = mild/moderate retentions; 2 = massive retentions) by use of VFSS and/or FEES. Besides clinical, VFSS and FEES examinations an MRI was performed following a standard protocol on a Siemens Magnetom Vision 1.5 Tesla.

Wallenberg's syndrome [17] was diagnosed when dysphagic patients showed the triad of ipsilateral Horner's syndrome, ipsilateral ataxia and contralateral hypalgesia [12] in the presence of a dorsolateral infarction of the medulla oblongata. Avellis' syndrome was diagnosed according to the criteria as described elsewhere [1, 14]. The brainstem atlas of Olszewski and Baxter [9] was used for the identification of brainstem nuclei and pathways. Nonparametric tests were applied (Kruskal-Wallis test, Mann-Whitney U test, Wilcoxon test); statistical significance was set at $p < 0.05$ and corrected according to the Bonferroni procedure.

Results

Sample characteristics and significant differences within and between patient groups are shown in Table 1.

Discussion

Although functional outcome showed a significant improvement after FST in each of the three groups, there were significant differences between them. Patients with WS had a better functional outcome as compared to patients with PFT or CH and a worse outcome as compared to patients with AS or PVN. 30% of WS patients were dependent on tube feeding after FST. This high percentage is in agreement with the results of other studies on WS patients who were admitted to a rehabilitation service. E.g., in the study of Meng *et al.* [6], 22% of patients with brainstem stroke remained dependent on tube feeding; in the study of Teasell *et al.* [15] even four of seven WS patients bearing a PEG (out of a total of 11 patients) could not resume oral intake at discharge. 18 of 27 patients with WS (66.7%) had bilateral pharyngeal retentions, which was described earlier by our research group [8] and other authors [2, 16] and may be ex-

plained by a disconnection syndrome between the ipsilateral pattern generators for swallowing and the contralateral side of the medulla, as proposed by Aydogdu *et al.* [2]. WS patients as well as those with PFT or CH had significantly more severe disturbances of UES opening and reflex triggering as compared to patients with AS or PVP. Therefore, besides FST, cricopharyngeal myotomy or botulinum toxin injection into the UES have to be considered in patients with WS, PFT or CH, especially in cases of severe and FST-resistant UES dysfunction as revealed by use of manometry. Finally, patients with PFT or CH showed a significantly more severely disturbed oral phase as compared to WS and AS patients.

It is worth mentioning that all WS patients had their infarctions in the most rostral part of the medulla. Our results point to the fact that the dorsomedial central pattern generators (DMCPGs) for swallowing, which are situated near the Nucleus tractus solitarii [7] and are affected in WS, are more important with regard to swallowing functions than the ventrolateral central pattern generators (VLCPGs), which lie near the Nucleus ambiguus and are affected, e.g., in patients with Avellis' syndrome. Since the outcome of patients with WS, with regard to dependence of tube feeding, was not associated with their lesion size or site, it may – due to the individual asymmetry of the swallowing-dominant forebrain hemisphere [4] – depend on the side of their medullary infarction.

As far as we know, this is the first study dealing with the outcome of dysphagic patients with PFT or CH. In the study of Perie *et al.* [10], only one patient with a longlasting ND due to CH was described. Based on our results it can be assumed that in these patients pressure is exerted on both DMCPGs in a posterior-anterior direction. Due to the importance of the DMCPGs for swallowing, bilateral (and often invisible) lesions seem to be very harmful. Hypothetically, the most severe ND would be found in patients with bilateral lesions of both DMCPGs and VLCPGs. Probably, such a "bilateral Wallenberg's syndrome" cannot be survived. For a better understanding of the pathomechanism responsible for ND in patients with PFT or CH, modern imaging methods such as proton magnetic resonance spectroscopy should be used for studying metabolic changes in the dorsal medulla in the future.

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Impaired self-awareness after moderately severe to severe traumatic brain injury

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Summary

Patients with moderately severe to severe traumatic brain injury (TBI) can demonstrate disturbances in self-awareness several months or years after injury. Patients may underreport cognitive and behavioral difficulties, which are the true residuals of their brain injury. Increasingly, research indicates that the residuals of these disturbances in consciousness greatly affect the process and outcome of rehabilitation. A recent model for conceptualizing disturbances of self-awareness after various forms of brain injury is reviewed.

Keywords: Anosognosia; impaired self-awareness; traumatic brain injury; outcome; rehabilitation; conceptual models.

Introduction

Neurosurgeons involved in the care of young adults with moderately severe to severe traumatic brain injuries (TBI) are often encouraged by the good neurological recovery made by many of these individuals. Patients may report to neurosurgeons and neuropsychologists fewer cognitive and behavioral difficulties than their relatives report about the patient. Patients' self-reports may create a false impression that they have made a better neuropsychological recovery than is actually the case [7].

Efforts at holistic neuropsychological rehabilitation have helped clarify that many patients with a history of moderately severe to severe TBI show residual impaired self-awareness [8, 11]. Working with TBI patients a mean of 1.5 years after their injury for 6 hours a day, 5 days a week, for 6 months led Prigatano and colleagues [16] to document the importance of disturbances of self-awareness on rehabilitation outcomes. For many years, however, whether this finding represented a psychological method of coping (i.e., denial) or an underlying neuropsychological disturbance was unclear. Data now appearing are helping to clarify the complexity of this problem and how it might best be approached. This article summarizes the current understanding of the problem of impaired self-awareness after moderately severe to severe TBI and offers a theoretical model to explain these disturbances.

Empirical observations on a subjective phenomenon

Impaired self-awareness, a disturbance in subjective experience, cannot easily be assessed with empirical methods [9]. Early attempts to do so involved patients rating their own level of competency in many areas. Based on clinical experience and using this methodology, Prigatano, Altman, and O'Brien [14] predicted that patients with moderately severe to severe TBI would tend to underestimate their difficulties with interpersonal interactions and emotional control but not their ability to care for themselves or to handle finances. This hypothesis was supported.

Prigatano [10] replicated the findings with a larger group of individuals. Fischer, Trexler, and Gauggel [2] again recently replicated this finding and noted the following: "Results from the PCRS* show that patients with orthopedic disorders underestimate, and patients with brain injuries (i.e., patients with TBI) overestimate their level of functioning in the total score and on the social and emotional subscale in comparison to staff ratings."

These and other cross-cultural observations [15, 19, 20] have led to a number of studies attempting to identify the neurological and neuropsychological markers underlying this disturbance. Somewhat ser-

* PCRS = Patient Competency Rating Scale (see Prigatano *et al.*, 1986).

endipitously, Prigatano and Altman [13] observed that TBI patients who finger tapped slowly also tended to underestimate their neuropsychological difficulties. Dikmen *et al.* [1] have demonstrated a "dose-response relationship" between speed of finger tapping and severity of TBI. These findings suggested that the severity of TBI may be related to residual problems of impaired self-awareness several months or years after injury.

Scherer *et al.* [21] reported a correlation of −.39 between the Glasgow Coma Scale (GCS) score and judgments of impaired awareness. That is, patients with higher scores demonstrated fewer problems with impaired awareness and vice versa. Prigatano *et al.* [15] obtained a similar finding in Spanish-speaking individuals. Collectively these findings suggest that the severity of TBI is related to impaired self-awareness even though traditional measures of neuropsychological dysfunction have not strongly related to measures of impaired awareness. Again, the only caveat is that patients who are lacking self-awareness tend to finger tap slowly.

Rehabilitation outcome and interventions

The importance of the problem of impaired self-awareness for rehabilitation outcome is becoming increasingly clear. Scherer *et al.* [21] demonstrated that impaired awareness was more predictive of gainful employment after TBI than many other factors, including severity or chronicity of TBI, the patient's preemployment status, preinjury use of alcohol, and a measure of overall cognitive dysfunction. This finding has been replicated by others and recently summarized by Prigatano [12].

As is true of many neurological conditions, understanding the nature of the problem does not automatically improve treatments. Understanding the etiology, however, is often the first step to doing so. Neuropsychological rehabilitation programs have evolved to attempt to deal with this problem of self-awareness [16]. TBI patients are engaged in a combination of both individual and group activities, which provide them an opportunity to compare their behavior to others and to obtain feedback about their strengths and limitations. Patients are guided to record and observe their behavior, and the feedback that they receive from multiple individuals helps them compare their personal observations with those of others. This process can offer modest help to some patients who are not fully aware of their neuropsychological difficulties. The process of TBI patients, who are themselves lacking in awareness, observing other brain dysfunctional patients' behavior can also help them to recognize that the other patients are not fully aware of their difficulties. Some patients can then grasp the logical implication that they too are not fully aware of their own difficulties. Such programs improve treatment outcomes and increase the percentage of patients who maintain work after a moderately severe to severe TBI [16, 18]. These findings have been expanded and replicated by Klonoff and colleagues [5].

A theoretical approach to the problem of impaired awareness after moderately severe to severe TBI

After the discovery that speed of finger tapping on the Halstead Finger Oscillation (Tapping) Test helps identify TBI patients with impaired self-awareness, the first step was to investigate patterns of brain activation when individuals performed this simple motor task. Normal individuals performing this task show activation in the ipsilateral cerebellum and contralateral sensorimotor cortex [4]. In some individuals the ipsilateral cerebral hemisphere and supplementary motor regions are also activated. Perhaps more interesting was the finding that individuals tended to show diffuse areas of bilateral activation when they fatigued while performing this task. No studies are available with large groups of TBI patients. However, a few case studies have shown that individuals with impaired self-awareness did not show this pattern of activation when they became fatigued while performing the Halstead Finger Tapping Test.

Johnson, Baxter, Wilder, and Prigatano [3] approached the problem from the perspective of self-reflection. Individuals were asked to reflect on their personal characteristics rather than on general information about themselves. Every normal individual showed mesial prefrontal activation with posterior activation of the cingular gyrus. These individuals also tended to show increased activation in the thalamus. This pattern may reflect a "channel" for accessing information about the self. These findings are compatible with the theoretical model that self-awareness is an emergent brain function distributed throughout multiple areas of the brain [8].

Mesulam [6] suggested that information registered by the paralimbic belt is near cortical regions that respond to multiple stimuli. The interaction between

the paralimbic and heteromodal cortical regions may allow self-awareness to emerge [11]. There may be partial and complete syndromes of impaired awareness (which consists of classic anosognostic syndromes). Patients often may show frank anosognosia that disappears with time. The explanation for this phenomenon remains unclear. However, after moderately severe to severe TBI, individuals can respond to the partial information obtained about the self with both defensive and nondefensive methods of coping. That is, some individuals with an underlying problem of impaired awareness may be defensive about how they describe their limitations while others may not. This general model has improved our appreciation of patients' subjective experience during neuropsychological rehabilitation [11].

Recently, Prigatano and Johnson [17] provided a theoretical model to place the problem of self-awareness into a broader framework regarding disturbances of consciousness after brain injury. In an exceptionally useful review, Zeman [22] distinguished three principal meanings of the term ''consciousness.'' First, consciousness can refer to the waking state. Second, it can refer to conscious experience in the here and now. Third, it can be used to refer to being conscious of another person's existence or mental state. Zeman provided the following examples of how the term consciousness may be used [22]: (1) ''After a lucid interval, the injured soldier lapsed into unconsciousness.'' (2) ''I am conscious of a feeling of dread and an overpowering smell of burning rubber.'' (3) ''I am conscious that I am straining your patience, (page 1266).''

After a TBI, the most obvious level of disturbed consciousness involves the sleep-wake cycle. Eventually, many patients return to a level of arousal equivalent to their premorbid functioning. However, they still may have disturbances in their experience of themselves. This state has been referred to as impaired self-awareness. We are also beginning to investigate their inability to perceive the mental state of others. There may be three vectors of human consciousness that interact and be disturbed after TBI, as discussed elsewhere [17].

Summary and tentative conclusions

Many young adults with moderately severe to severe TBI appear to make a good neurological and neuropsychological recovery. Upon questioning they may report few neuropsychological or behavioral difficulties. Yet many of these individuals remain unemployed and have difficulties maintaining work and interpersonal relationships. Intensive efforts at neuropsychological rehabilitation have suggested that these individuals may suffer from disturbances of self-awareness. Behavioral studies and recent neuroimaging studies suggest that this disturbance involves frontal limbic connections crucial for normal social interaction and judgment. By understanding these problems, true residuals of anosognosia can be distinguished from denial as a psychological defense. Moreover, these phenomena are extremely important for designing effective neuropsychological rehabilitation programs and for developing a comprehensive theory of consciousness.

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Assessment of health-related quality of life in persons after traumatic brain injury – development of the Qolibri, a specific measure

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Summary

Background. Health-related quality of life (HRQOL) associated or not with the measurement of neuropsychological functioning is a relatively new outcome variable in the field of traumatic brain injury (TBI). In both cases, accuracy and precision are increased in outcome estimation. Validation of generic, cross-culturally (cc) administered HRQOL measures in persons after TBI is not yet well established. Disease-specific HRQOL instruments do not exist in an international context. The objective here is to present the TBI consensus group's (QOLIBRI-Group) approach in cc development of a specific HRQOL measure – the QOLIBRI (Quality of Life after Brain Injury).

Methods. Special issues of TBI-specific instrument creation will be highlighted as well as cc questionnaire construction, development, translation and psychometric testing.

Results. The validation process of the preliminary version of the disease-specific QOLIBRI in 15 countries and 13 languages will be described. The QOLIBRI assesses HRQOL within six domains (physical condition, thinking activities, feelings and emotions, functioning in daily life, relationships and social/leisure activities, current situation and future prospects). The QOLIBRI integrates disease-specific issues of TBI patients, i.e. cognition, existential aspects (as the sense of self) etc., which are missing in generic tools.

Conclusion. In TBI patients, generic and disease-specific aspects of HRQOL need to be assessed with measures of adequate psychometric quality, applicable across different populations and cultural conditions. The QOLIBRI is a promising instrument for sensitive patient-centered specific outcome evaluation after TBI.

Keywords: Traumatic brain injury; outcome; health-related quality of life; neuropsychological; generic; disease-specific; assessment.

Introduction

Background

During the last thirty years, health related quality of life (HRQOL) has been introduced as a primary outcome variable in medicine, and recently in the field of traumatic brain injury (TBI). Current health status and HRQOL measures will be identified, and their validity for application in persons after TBI evaluated. Health status instruments determine an individual's perceived level of functioning in four or five different dimensions of life (see below). Most HRQOL measures additionally assess feelings of well-being concerning these QOL dimensions. HRQOL instruments contribute to quality control in daily practice, clinical research, and decision making. Most questionnaires cover several dimensions by a number of items, which are associated with different subscales. Subscale scores are often compiled into one (sum score) or a number of subscales (profile).

In the early eighties HRQOL has been distinguished from the more general, non-HRQOL concept which investigates self-rated QOL with respect to nutrition,

environment, traffic etc. [32]. HRQOL represents a person's perspective on his or her subjective health condition, treatment, functioning and well-being in the domains of physical, psychological (emotional and cognitive), social and daily life [41]. The WHOQOL-Group [37] expands upon the WHO's definition of health and the definitions of HRQOL generally in use, by stressing the fact that a person's QOL auto-evaluation is embedded in his or her social, cultural and environmental context, and that this has to be reflected in the content of assessment. The measurement of this multidimensional HRQOL construct is usually acquired via self-rating; since the latter, however, involves intact or partly intact cognitive functioning, in certain cases – such as in persons with severe dementia with a Mini Mental State score below eight [15] or TBI with severely impaired cognition – the measurement needs to be performed by observers (proxies) [39, 40].

A comprehensive HRQOL evaluation e.g. in clinical and health economic studies should generally include psychometrically sound generic and specific HRQOL instruments. Generic measures do allow investigations of different QOL dimensions in a general way in healthy as well as unhealthy populations, as these measures do not take into account a person's specific health condition. Disease-specific HRQOL measures in comparison are sensitive for a specific health condition. Their application in clinical, quality and utility trials is favored by some professionals working in the field, related to the more focused, precise information gain. Disease-specific HRQOL instruments do not, however, allow the comparison of different disease conditions.

Neurology and neurosurgery have been adapting HRQOL as a patient-centered outcome relatively late. A literature search in PubMed (1964 to 2004) returns more than 60 000 publications for the keyword HRQOL. For the combined keywords "HRQOL" and "TBI" the search shows 132 hits in Pubmed (1964 to 2004) and 103 in PsychInfo, in total 201 (corrected for double citations) all published during the last 10 to 15 years. For "HRQOL", "TBI" and "cognitive impairment" only four publications are indexed in Medline and four further in PsychInfo.

In a review on HRQOL outcome estimation in patients after TBI, Dijkers [11] requests the validation of psychometrically well-tested generic HRQOL tools in this population and the study of the meaning of cognitive and functional limitations for patients after TBI. The author underlines the fact that the impact of TBI on QOL regarding negative affects, negative mood and losses are rather well researched, that positive aspects, however, as creating a new life after TBI, are not evaluated with existing HRQOL tools. This is an important observation, which holds especially true for most disease-specific instruments and it implies the need for complementary assessment of positive aspects of well-being, along with the negative symptoms [40, 41].

Although research has started to address HRQOL in TBI patients, validated instruments have not yet been widely used [7]. The most frequently administered generic measures are the Short Form 36 (SF-36, e.g. 14, 25, 43) and the Sickness Impact Profile (SIP, 9, 35). Most studies which have used the SF-36 and the SIP found lower scores on all subscales for people after TBI than for those without. Validity problems are pointed out by v. Steinbuechel [6, 40, 41] and by Riemsma [31] in an extensive review on health status instruments administered in patients with cognitive deficits.

The development of disease-specific HRQOL measures in TBI patients is very recent. Pirrente and collaborators [29] developed an instrument which evaluates four dimensions of QOL (physical, social, symptoms, and psyche) in persons after TBI; however, this instrument is neither yet fully validated in German TBI populations [29] nor cross-culturally (cc) in European and Asian languages. The European Brain Injury Questionnaire – EBIQ [34] can be considered as a first successful cc approach in brain injury, assessing the subjective experience of patients after a brain injury [7]. It does, however, not explicitly measure HRQOL in TBI.

The aim of this paper is to present steps of an international consensus group in the development and validation of a specific HRQOL tool for persons after TBI, targeting at their particular health condition which is generally accompanied by cognitive impairments, and b) in the cc validation of this questionnaire.

Methods

Most HRQOL measures were developed in a particular language and cannot be simply translated to another language or used in a different cultural group. When questionnaires are to be available in different languages for cross-cultural (cc) use, the construction, translation, psychometric testing, and norming have to follow certain rules [5, 7]. Equivalence between different language versions is necessary and requires a complex translation procedure, to ensure cc comparability of the measure [20]. Generic HRQOL instruments, as

e.g. the SF-36 Health Survey, the SIP, the Nottingham Health Profile and the WHOQOL [37], fulfill these requirements. Most of these [5, 7], as e.g. the SF-36 and the SIP, have been first developed in one language (predominately in US English) and then sequentially translated in various other languages. In contrast, the WHOQOL was developed simultaneously by a consensus group of experts from over 20 countries, selecting the domains and items on the basis of focus group work in the respective countries who formulated the single items simultaneously. The cancer-specific EORTC instrument, in contrast, represents a parallel approach, selecting items from available questionnaires developed in different languages.

The reformulation, selection and translation process as well as psychometric and norming work are performed similarly in all approaches. Guidelines for the translation of measures [1] usually require one or two forward translations from the original into the target language by independent translators: the two versions are then integrated into one. In a third step, an independent native speaker translates this version back into the original language. All translated versions and the original are simultaneously compared on the item level. Following these constraints, cc validity of the items may be obtained. Equivalence of the different language versions has to be proven by functional, operational, scale, and metric equivalence testing across countries [5, 20]. For psychometric testing of all versions, questionnaires have to be filled out by a sufficient number of persons per country (a number, typically about twice to fourfold the number of original items). Reliability, validity (confirmatory, discriminate and convergent), accuracy and suitability have to be tested cc, and sensitivity in longitudinal, e.g. clinical trials (for psychometric criteria see e.g. Riemsma [31]). To arrive at representative norms, representative population groups – usually over ten thousand participants – have to participate in the validation studies.

One of the special psychometric issues concerning the quality of generic or disease-specific self-rated HRQOL questionnaires for patients with cognitive impairment, namely TBI, is their proper validation. Is this specific questionnaire e.g. appropriate, important and applicable to TBI-patients? Little is also known about the cognitive skills required to rate the different HRQOL domains adequately. Unawareness of cognitive deficits and changes of the self may interfere differently with ratings of the cognitive, emotional or the physical scale. Separate analyses should be performed to assess the validity of an instrument for different levels of cognitive impairment and anosognosia. Changes of the reference level of the ratings due to changes of identity as a consequence of an adaptational process to TBI have to be taken into account. Response-shifts have to be investigated in longitudinal studies. In cases of severe deficits due to the sequelae of TBI validated proxy-ratings could be of use.

Results

Neugebauer was one of the first researches to formulate the need for development of a disease-specific cc HRQOL tool in multiple trauma [27]. In 1999 he therefore initiated an international TBI consensus group (TCG) and the development of such a tool. This process comprises of several steps, which were elaborated in six consensus conferences: Cologne 1999, Paris 2000, Windsor 2001, Paris 2002, Amsterdam 2002, Geneva 2003.

The TCG first provided an overview on self-rated outcome measures administered in TBI patients all over the world, and reviewed them taking their appropriateness, psychometric quality, etc., into account for cc HRQOL evaluation. The TCG agreed on a new approach, which can be called a parallel/consensual approach, distinguished from the sequential (i.e. SF-36), simultaneous (i.e. WHOQOL) or parallel (i.e. EORTC) method. The TCG identified, examined and selected measures available in different countries. Most of the authors of potentially adequate questionnaires participated in the TCG, supplying insight into the underlying concepts, and providing psychometric data and applications. The following instruments were selected: the Quality of Life of the Brain Injured [38], the Profile de la Qualité de la Vie Subjective [18, 36], the Brain Injury Community Rehabilitation Outcome Scale [30], and the European Brain Injury Questionnaire [10, 34].

In a further step (Paris 2002), items existing or translated into English (if only existing in another language) were compared across measures. Via expert consensus, generally based upon – among other criteria [27] – the evaluation of psychometric properties, the most pertinent for TBI were selected for the new measure from the total data pool (148 items). The experts – 15 neurosurgeons, neurologists, neuropsychologists, psychologists and other health care professionals working, e.g., in neuro-rehabilitation – attributed the selected items to seven QOL dimensions, based on a systematic literature review and the underlying questionnaire structures: physical condition, thinking activities, feelings and emotions, functioning in daily life, relationships and social/leisure activities, existential domain, current situation and future prospects [4, 7]. These were compiled, reanalyzed, and some were reattributed to the remaining six scales by J. Powell and N. von Steinbuechel, and the existential domain was eliminated, for lack of items. As the item formulations and answering modes differed for the questionnaires, one mode was suggested. There is a tendency observable in HRQOL assessment to concentrate on negative symptoms and adverse events; an explicit evaluation of positive aspects of well-being is frequently missing. Since the mere missing of negative ratings is not automatically implying good or satisfying QOL, the answers to the items were formulated in the form of satisfaction ratings. This measure was then reviewed by all TCG participants and revised by A. Mass and collaborators for the fifth consensus conference in Amsterdam in 2002. Here, 79 pre-final items, either formulated as satisfaction (“How satisfied

are you ...'') or as bothered (''How bothered are you ...''), were chosen. This TBI-specific HRQOL measure was named QOLIBRI (quality of life after brain injury).

According to translation guidelines [1], the QOLIBRI was translated and tested in 15 countries. After translation, cognitive debriefing [7] was performed: in five TBI patients and five lay persons per country, the clarity of the concept, understandability, wording, relevance, appropriateness of item formulation, and adequacy of instrument length and missing domains were assessed. The individuals filled out the questionnaire and were then interviewed with respect to these criteria. Per country a synopsis of the cognitive debriefing was elaborated. All results and reformulation suggestions of each country were summarized per item by the methodological center in Geneva. During the last consensus conference in Geneva (2003), representatives from nearly all participating countries decided upon the field version of the QOLIBRI on this basis. The final version with 56 items went into field testing, after final harmonization of the translations of all new or differently formulated items (via telephone conference). This cross-sectional field testing of the QOLIBRI is embedded in a complex validation protocol, assessing medical, psychological and socio-demographical data; this will be described elsewhere in detail.

This final field version contains 56 items, including overall QOL ratings of each subscale/domain (physical condition, thinking activities, feelings and emotions, functioning in daily life, relationships and social/leisure activities, current situation and future prospects); 42 are summarized in these six subscales and rated via a five-point satisfaction rating. Thirteen items investigate how bothered the individuum feels by negative symptoms, facts and circumstances associated with TBI. These thirteen items are listed under the following five subscales: physical conditions, feelings, functioning in daily life, current situation and future prospects and one overall rating of their feeling bothered by certain consequences related to TBI is added. Specific issues for persons after TBI as fatigue, sleep, difficulties with cognition and controlling emotion, self-awareness, self-image, achievement after brain injury and future projects, etc., characterize this questionnaire. In September 2004 first statistical analyses including the procedures mentioned by Bullinger (1994) and Riemsma [31] were performed by the methodological center and presented during a QOLIBRI workshop in Rome (2004).

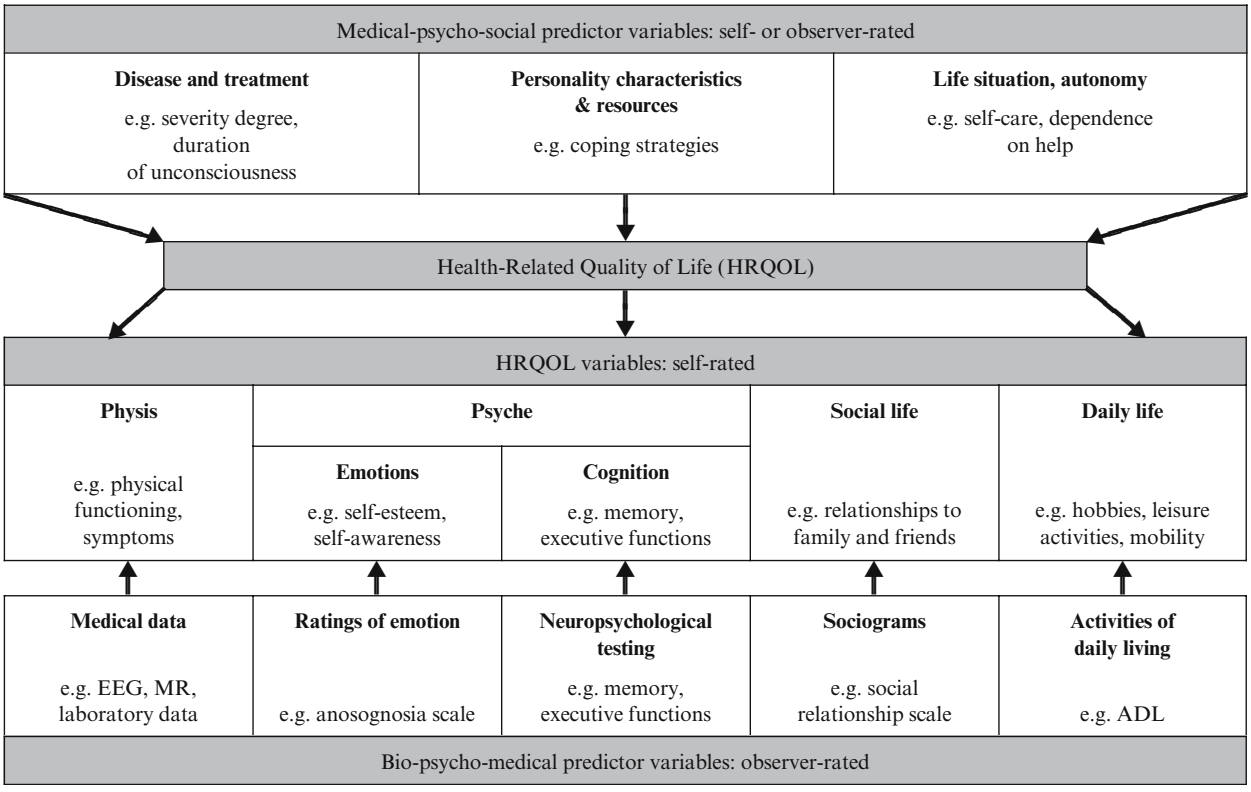
To give a flavor of possible psychometric properties of this new tool, very preliminary analyses of a German data set ($N = 86$) show adequate psychometric characteristics and seem to support the assumed structure of the instrument and its subscales. Reliability (Chronbach's Alpha) for the subscales, rated via satisfaction, ranges from .75 to .95. The ''bothered by'' items are not yet analyzed. Test-retest correlation is above .73 for all scales. Rather high subscale intercorrelations (r between .54 and .79 for all subscales) are found. Convergent correlations with the anxiety scale of the Hospital Anxiety Depression scale (HAD, 7) show coefficients between $-.37$ and $-.68$, and for HAD depression scale coefficients between $-.60$ and $-.74$. No gender or age differences are found for the QOLIBRI scales. Testing of all complete data sets will reveal the cc properties.

Summary and outlook

What is important for an individual's well-being after TBI, and how to assess the subjective QOL of these patients, have become important questions for health care professionals and researchers [28, 42]. A prerequisite to cc assessment of the reality and whishes of these individuals, the costs, the effects of the disease, treatment, care and rehabilitation on mental as well as physical functioning and well-being (HRQOL), is the availability of appropriate tools.

Generic questionnaires still need extensive validation [11, 31] in this field. Here, we presented important steps in the development of a TBI-specific HRQOL questionnaire, the QOLIBRI. The preliminary version contains 56 items which have been carefully selected and revised according to the cc validation criteria outlined above to maximize content validity. To our knowledge, the QOLIBRI questionnaire is the only specific HRQOL tool in TBI appropriate for cc use with promising psychometric quality. Reliability, validity and equivalence testing now need to be assessed via cc psychometric analyses. Sensitivity and clinical relevance will be evaluated in several upcoming longitudinal studies. Additionally to validity and reliability testing in larger TBI populations, this new instrument will be tested for differences to generic HRQOL questionnaires and the relevance of these potential differences in clinical practice. Further information is needed to estimate the additional gain or advantage in using this behavior-oriented instrument in comparison to more traditional injury-related outcome predictors

Table 1. *Bio-psycho-social measurement model of HRQOL in persons after traumatic brain injury*



(Adapted from N. v. Steinbüchel, 1996).

or estimates. Examples for the latter are the Glasgow Coma Scale (GCS, 33), the length of impaired consciousness and duration of posttraumatic amnesia [3], type of lesion [17], pupillary responses and age [23], Glasgow Outcome Scale (GOS, 21), and the FIM [19]. Last but not least the impact of neuropsychological dysfunction on this new instrument needs to be investigated.

To further test the validity of the QOLIBRI in the application to persons after mild, moderate or severe TBI, validated, standardized, comprehensive neuropsychological batteries should be added to the measurement protocol. In spite of the heterogeneity in neuropsychological outcomes (e.g. 8, 13, 19, 22), most studies, however, observe deficits in processing and motor speed, in memory, attention, discourse and emotional functions [13, 26]. Cognitive impairment after TBI can predict or indicate functional integration [16] and QOL [11, 22–24, 31]. When interested in valid estimations of HRQOL in persons after TBI, the complementary assessment of neuropsychological functioning therefore seems indispensable. Only with coordinated tools, including self- and observer-ratings of all dimensions of QOL and their predictors – especially the explicit subjective and objective assessment of the cognitive domain – estimation of HRQOL will be comprehensive and valid in this population. Table 1 summarizes a conceptual model that enlists variables and areas which are crucial for a valid and comprehensive coverage of HRQOL after TBI.

HRQOL needs to be assessed in four areas: physis, psyche, social life and daily life (center line in Table 1). In the psychological domain emotional and cognitive aspects have to be assessed explicitly [6, 40, 41]. Relevant predictor variables (first and third row) should be measured along with the self-rated core HRQOL variables. Only in cognitively severely impaired persons after TBI, observers (proxies) should serve as raters.

Thorough conceptual and psychometrical analyses regarding the association of variables – e.g. neuropsychological and HRQOL data – have to be performed in order to improve validity of HRQOL assessment in persons after TBI. The suggested comprehensive measurement could provide a valuable basis in responding to the need for more patient-centered

generic and disease-specific well validated HRQOL outcome assessment in the field of TBI.

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B. Re-engineering of brain lesions

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RNA editing: a molecular mechanism for the fine modulation of neuronal transmission

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Summary

The term ''RNA editing'' is used to identify any mechanism responsible for producing mRNA molecules with sequence information not specifically encoded in the DNA.

RNA editing is therefore an important event in gene modification, which takes place at a post-transcriptional level. The molecular mechanism of RNA editing involves site-selective deamination of adenosine to inosine in pre-mRNA, which leads to altering translation codons and splicing in nuclear transcripts, whereby functionally distinct proteins can be produced from a single gene. The mammalian editing enzymes ADARs (adenosine deaminases acting on RNA) are widely expressed in brain and other tissues: however, up until now their substrates have mainly been found in the Central Nervous System (CNS). Of particular relevance in the CNS is the editing occurring at the ionotropic glutamate receptors (GluRs) level. Three AMPA and two Kainate receptors are subject to RNA editing. The consequence of this process is the substitution of specific amino acids in functionally critical positions of the receptors. Depending on the GluR involved, the consequences of editing will involve: activation and/or inhibition of splicing sites; modulation of the trafficking of the receptor to the plasma membrane; the process of tetramerization of the receptor subunits; modification of the ions passage through the receptor channel; modulation of the desensitization and action potential recovery times. All these events are specific to the different GluRs and are genetically and developmentally controlled.

RNA editing is therefore a crucial event involved in controlling transmission of the action potential at the postsynaptic level. This modulation involves the transmission of all sensory stimuli to the CNS and gives rise to the ''Sensotype''. The Sensotype therefore defines the ''way'' in which the information acquired from the environment by the sensory systems is transmitted to the brain. The signals and inputs deriving from the Sensotype are transmitted to the brain, which processes and stores these signals thus generating the ''Brainotype''. Brainotype and Sensotype are genetically and environmentally determined; they are individually unique and specific to every living organism with a nervous system. Their characteristics are, at least in part, dependent on the modulation of the ''RNA editing'' process since glutamate receptors represent the main neurotransmitter system in the CNS.

Keywords: RNA editing; glutamate receptors; serotonin receptor; sensotype; brainotype.

Introduction

The term ''RNA editing'' is used to identify any mechanism responsible for producing mRNA molecules with sequence information not specifically encoded in the DNA.

The term was first used to described the insertion of single uridines in mitochondrial RNA of trypanosomes [6], but now it refers to any site-specific alteration in an RNA sequence, excluding changes due to RNA splicing, capping or polyadenylation (for review see: 2, 14, 21, 29, 32–34).

This post-transcriptional mechanism result in protein diversity through alteration in start and stop codons, frame shift and single amino acid changes at functionally important positions. In mammals, pre-mRNA editing involves the deamination of cytidine (C) or adenine (A) forming uridine (U) and inosine (I) respectively.

Mammalian C-U editing

The mammalian apolpoprotein B, a component of the plasma lipoprotein for the transport of cholesterol and triglycerides, is subject to C-U RNA editing [28]. The canonical isoform, APOB100, is expressed in the liver and in the small intestine. In the latter tissue the APOB mRNA is subject to specific deamination of a citidine, at the nucleodite position 6666, which, following editing, will change a glutamine into a translation stop codon. The reaction leads to the expression of a shorter isoform, the APOB48, that loses the C-terminal domain and is utilized for the synthesis and secretion of chylomicrons [28]. The specific tissue ex-

pression of APOB48 is due to the fact that the enzyme that catalyzes the editing reaction (APOBEC1) is only present in the small intestine. The enzyme recognizes on the pre-mRNA a 20-nucleotide sequence, the ''mooring sequence'', localized exactly 4 nucleotides from the editing site, and, by the combination with other proteins, catalyzes the editing reaction [14, 21].

Mammalian A-I editing mediated by adenosine deaminases

In addition to C-U substitution the most widely studied nucleotide change due to RNA editing, in mammals is the modification of a specific adenosine to an inosine in the pre-mRNA of several genes expressed in the central nervous system. The inosine is then recognised by the translational protein machinery as a guanosine, leading to a modification of the amino-acid coded by the edited codon.

At present, three enzymes that catalyse the A-I editing reaction have been characterized. They all belong to the family of adenosine deaminases acting on the RNA (ADAR). These enzymes present one or more RNA-binding domains at the C-terminal catalytic domain and a variable N-terminal domain. ADAR1 and ADAR2 are expressed in many tissues but mainly in the brain; ADAR3 is expressed only in neuronal tissues but its role in the editing reaction has not yet been characterized. A possible function of ADAR3 might be to act as an inhibitor of ADAR1 and ADAR2, thus competing for the editing substrates [2].

Site-specific deamination of adenosine to inosine depends on the secondary structure of the pre-mRNA. The RNA structure involved in editing seems to be due to a strong affinity between the exonic sequence that carries the editing site and an intronic sequence, defined as the ''editing complementary sequence'' (ECS), which may be localized several kb from the editing site and shows sequence complementarity with the exonic sequence. The importance of the ECS is demonstrated by its high conservation through evolution and among species [34].

Editing of glutamate receptors

The most frequently characterized A-I editing sites are present in ionotropic glutamate receptors (iGluRs).

Fast excitatory neurotransmission in the vertebrate central nervous system is mainly mediated by iGluRs, which can be divided into NMDA (N-methyl-D-Aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid) and kainate receptors on the basis of selective agonist activation, pharmacological characterization and sequence similarity [9, 11].

Mammals express four AMPA (GluR1–4), five kainate (GluR5–7, KA1, and KA2) and six NMDA (NR1, NR2A-D and NR3A) receptor subunits. In addition, two δ subunits (δ1 and δ2) have also been found, but their function is as yet unknown [25]. Five of these subunits might be altered by RNA editing.

In the case of the AMPA GluR2 subunit and the kainate GluR5 and GluR6 subunits, deamination results in the substitution of a codon for glutamine (C<u>A</u>G) with a codon for arginine (C<u>I</u>G) in the membrane domain M2 of the receptor channel, at the so-called Q/R site. The presence of arginine, a positively-charged amino acid, in the inner channel pore gives the receptor channel reduced Ca^{2+} permeability [12], reduced ion conductance [36] and altered current/voltage relation [19].

In the normal brain virtually all pre-mRNAs encoding GluR2 are edited at the Q/R site, whereas the other AMPA receptors are not edited at this site. Moreover, Q/R editing critically determines the maturation and cellular trafficking of GluR2 [15]. The GluR2 Q/R edited form is retained in the endoplasmic reticulum (ER) because the post-transcriptional codified arginine, located in the pore loop, provides a major retention signal and favours the association with specific retention factors. Trafficking to the cell surface might be allowed only for fully assembled, hetero-tetrameric receptors in which the retention signal is masked by the presence of other GluRs subunits [16].

GluR2, 3 and 4 are edited at the R/G site, where a codon for arginine (<u>A</u>GA) is modified into a codon for a glycine (<u>I</u>GA); this site is located just before the sequences involved in the splicing events forming the so-called Flip/Flop isoforms and it seems to affect both the splicing events and the desensitisation properties of the AMPA receptor channels [24, 26].

Finally, while the kainate receptor GluR5 [3] can be edited only at the Q/R site, the kainate GluR6 [4] can be edited at other two sites: the I/V and Y/C sites are located in the transmembrane 1 domain (TM1) where an isoleucine (<u>A</u>TT) is modified into a valine (<u>I</u>TT) and a tyrosine (T<u>A</u>C) into cysteine (T<u>I</u>C), respectively. These editing sites may be involved, toghther with the Q/R site, in a finer regulation of ion permeability [22].

Unlike GluR2, Q/R editing levels of GluR5 and GluR6 kainate receptor subunits are developmentally regulated [7] and the extent of kainate receptor editing in different brain regions appears to be regionally regulated [5, 8].

The importance of editing levels in the properties of GluR receptors has been shown by the data obtained in knockout mice. Mutant mice, in which the GluR2 ECS sequence has been eliminated [10, 13] or the editing enzyme ADAR2 [18] suppressed, showed a sharp drop in Q/R editing levels and an altered ionic permeability and they were prone to epileptic seizures leading to death after a few weeks from birth. Moreover, these knockout mice displayed nuclear accumulation of incomplete spliced GluR2 pre-mRNA and decreased levels of GluR2 mRNA. The increase in unspliced GluR2 pre-mRNA was correlated with the Q/R site reduction editing level, thus suggesting that editing might be a requirement for efficient splicing of the pre-mRNA [18]; on the other hand mutant mice in which a constitutive arginine is present at the GluR2 Q/R site show a vital phenotype [20].

Knockout mice in which the GluR6 ECS [37] had been deleted showed that unedited GluR6 may mediate synaptic plasticity and that the edited GluR6 receptors may reduce seizure vulnerability.

On the contrary, GluR5 mutant mice carrying a constitutive arginine (R) instead of the genomically encoded glutamine (Q) at the editing site do not exhibit developmental alteration or abnormal behaviour [30]. The editing reaction of this receptor may well be involved in superior mechanism such as learning and memory but it is not necessary for survival.

Editing of serotonin receptors

In the central nervous system the serotonin receptor (5-HT-2c) can also be edited in five closely spaced positions (A, B, C, C′, D) that alter the amino acid sequence of the second cytoplasmatic loop. 5-HT-2c is a GTP-binding protein-coupled receptor that modulates phospholipase C activity and ultimately regulates Ca^{++} inflow. Theoretically, 24 different receptor protein isoforms could be encoded and a pool of editing variants expressed in both rodent and human brain [31, 32]. The different editing variants show a different level of PLC activation. RNA editing in the five positions on 5-HT-2c receptor leads to a very fine regulation of serotoninergic neurotransmission.

Editing and diseases

The importance of the editing reaction in the physiology of the nervous system raises the hypothesis that its malfunction may be implicated in several neurological disorders.

Indeed, the editing levels of the serotonin receptor were found to be reduced in patients suffering from schizophrenia [35] and increased in suicides [27]. As regards glutamate receptors, the editing levels of the GluR2 Q/R site have been found to be altered in the cerebral cortex of patients suffering from schizophrenia, Alzheimer's and Huntington's disease [1]. In addition, the editing level of GluR6 increases in patients with temporal lobe epilepsy [17, 23]. These findings, although preliminary, show that the editing reaction might be involved in neurological disorders.

Concluding remarks and definition of "sensotype" and "brainotype"

RNA editing of neurotransmitter receptors is considered an important mechanism in generating protein diversity and it may profoundly affect neurotransmission, being a crucial event involved in controlling the transmission of the action potential at the postsynaptic level.

In particular, the editing level of different GluRs is:
- genetically and developmentally determined;
- specific to the different GluRs;
- specific to the different areas of the central nervous system (similar mechanisms apper to be present and regulated also in the peripheral nervous system – PNS- as well);
- variable, depending on the editing site involved;

GluR RNA editing seems to be recent in evolution; it appears after the separation of non-mammalian vertebrates (Aghnata) and vertebrates with spinal column and cranium (Gnathostome) and it might be involved in the evolution of superior functions such as learning and memory.

The RNA editing reaction therefore influences the receptors' structure and function, acting at different levels: RNA editing modulates RNA splicing of several glutamate receptors (our manuscript in preparation); Q/R RNA editing modulates receptors transport from the endoplasmic reticulum to the plasma membrane [15] and mediates GluR subunits tetramerizzation [16]; at the functional level RNA editing

modulates ionic transport through the GluR receptor channels; R/G RNA editing modulates desensitization and the recovery time of GluR receptors [24].

On the basis of these data, it is clear that the physiological changes induced by an action potential on the postsynaptic membrane of glutamatergic synapses are dependent much on the editing reactions.

RNA editing, in association with the other mechanisms involved in the fine modulation of neuronal transmission, therefore plays a crucial role in determining *the ''way'' in which the information acquired from the environment, by the sensory system, is transmitted to the brain*. This complex process, involving the modalities of acquisition and transmission of the sensory inputs by the PNS, has been defined with the new term: *''Sensotype''*. The Sensotype is genetically and developmentally determined and is unique and specific to every form of life with a nervous system.

The signals deriving from the Sensotype give rise, in the CNS, to the *''Brainotype''* which corresponds to *the ''way'' in which the brain processes and stores the stimuli deriving from the Sensotype.* The Brainotype is also individually unique and depends on the genotype, on environment and on personal experiences. Simply stated, the Brainotype defines the combination of the personal genotype with the personal history and experiences.

The right balance between ''Sensotype'' and ''Brainotype'' is required for normal function; alteration in the ''Sensotype'' may cause alteration in the ''Brainotype'' and *vice versa*. RNA editing may be one of the factors involved in the control of this balance which modulates the responses to and the processing of the external stimuli, particulary as far as superior functions are concerned.

The combination of Brainotype and Sensotype can be considered equivalent to the ''SELF'' which may therefore, at least in part, depend on the modulation of the ''RNA editing'' process and contribute to its uniqueness.

Sensotype and Brainotype cannot be cloned!

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Inhibition of IκBα phosphorylation prevents glutamate-induced NF-κB activation and neuronal cell death

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Summary

NF-κB is a nuclear transcription factor involved in the control of fundamental cellular functions including regulation of cell survival. We investigated NF-κB activation induced by two opposing modulators of cell viability: IL-1β and glutamate. We found that IL-1β activated p50, p65 and c-Rel subunits of NF-κB, while glutamate activated only p50 and p65 proteins. Cell stimulation by glutamate, correlated with expression of the pro-apoptotic genes Caspase-3, Caspase-2L and Bax. Conversely, IL-1β induced the expression of the short anti-apoptotic isoform of Caspase-2. Finally, we analysed the effect of the inhibition of IκBα degradation on glutamate-induced toxicity by using BAY 11-7082, a selective inhibitor of IκBα phosphorylation. Our results suggest that BAY 11-7082 preserves neuron viability from the glutamate-mediated injury.

Keywords: Glutamate; IL-1β; Bay 11-7082; NF-κB, p65.

Introduction

The transcription factors NF-κB have been shown to function as key regulators of either cell death or survival in neuronal cells. They consist of homo- or heterodimeric complexes belonging to the Rel family, composed of five members, including p50, p52, p65/RelA, RelB and c-Rel. In the central nervous system, NF-κB proteins are ubiquitously expressed in neurons and glia [15], where they are involved in physiological processes as well as in acute or chronic neurodegenerative disorders like brain ischemia [20], spinal cord trauma [2], Parkinson's disease [8] and Alzheimer's disease [21]. Nevertheless, the role of NF-κB in neurodegeneration is still controversial: data supporting a pro-survival effect of this transcription factor [11, 13, 14] are opposed by evidences demonstrating a death promoting role of NF-κB proteins [3, 6, 19, 20, 22].

In a previous study [18], we showed that selective activation of diverse NF-κB family members may lead to distinct effects on neuron viability. Both in cultured rat cerebellar granule cells and in mouse hippocampal slices, we examined NF-κB activation induced by two opposing modulators of cell viability: interleukin-1β (IL-1β), that promotes neuron survival, and glutamate that induces cell death. We found that IL-1β stimulates NF-κB factors by inducing both IκBα and IκBβ degradation, while glutamate induces a delayed and transient activation of NF-κB, associated with the specific loss of IκBα. Moreover, the toxic effect of glutamate is associated with activation of p50 and p65 NF-κB factors, while the neuroprotection by IL-1β requires activation of c-Rel. In this work we investigated whether the opposite regulation of cell survival by glutamate and IL-1β correlates with a different regulation of pro- and anti-apoptotic gene expression. Besides, we investigated the effects of the inhibition of IκBα degradation, by a selective inhibitor of IκBα phosphorylation, on neuron susceptibility to glutamate.

Our results suggest that excitotoxicity induced by glutamate is associated with activation of p50/p65 NF-κB dimer and induction of pro-apoptotic genes. Drugs which prevent IκBα degradation preserve neuron viability from the glutamate-mediated injury.

Materials and methods

Experimental models

Primary cultures of cerebellar granule cells were obtained from dissociated cerebella of 8-day-old Sprague Dawley rats and cultured as previously described [17].

Ribonuclease protection assay (RPA)

Cerebellar granule cells were treated for 20 min with 250 U/ml IL-1β and for 15 min with 50 μM glutamate. After 1 hour, whole-cell

RNA was isolated using the Tri Reagent method (Sigma-Aldrich), extracted using chloroform-ethanol according to the procedure suggested by the manufacturer and stored at −80 °C. Apoptosis gene expression was determined by Ribonuclease Protection Assay (RPA). Riboquant Multi-Probe RNAse Protection Assay is a commercial kit (Becton Dickinson PharmaMingen) for detecting and quantifying rat Fas antigen, Bcl-x, FasL, MnSOD, Caspase-3, Caspase-2L, Caspase-2S, Bax and Bcl-2 mRNA. Templates were used to generate a ^{32}P-labeled anti-sense RNA probe set and hybridized in excess to target RNA. Total RNA (5 μg) was hybridized with the labelled probe sets followed by RNAase treatment and analysis of protected bands on a denaturing 5% polyacrylamide gel. Gels were exposed to x-ray films for 7 days and bands were quantified by densitometry. Relative mRNA levels were calculated by normalizing to the ribosomal RNA L32 and GAPDH bands included in the set of probes, as the housekeeping RNA.

Nuclear extracts preparation and electrophoretic mobility gel shift assay (EMSA)

Nuclear extracts from primary cultures were prepared according to a small scale protocol [1] 45 min after glutamate pulse. EMSA and supershift analysis were carried out as previously described [18].

Results

Glutamate, but not IL-1β, activates pro-apoptotic genes in rat cerebellar granule cells

Glutamate and interleukin-1β (IL-1β) are two opposing modulators of cell viability, as glutamate causes cell death while IL-1β promotes cell survival in primary neuronal cultures [18]. We studied the composition of the NF-κB complexes activated by glutamate and IL-1β in rat cerebellar granule cells. By using selective NF-κB antibodies for their ability to interfere with DNA binding activity, we found that distinct NF-κB proteins are involved in the opposing modulation of cell survival elicited by glutamate and IL-1β. As extensively described by Pizzi *et al.* [18] and shown in Table 1, glutamate preferentially induced NF-κB dimers composed of p50 and p65 proteins, whereas IL-1β activated NF-κB dimers composed of p50, p65 and c-Rel subunits.

We then investigated whether NF-κB activation and regulation of cell survival elicited by glutamate and IL-1β, might involve a differential activation of pro- and anti-apoptotic genes. RPA analysis of apoptosis regulatory genes showed that glutamate induced a significant increase of the pro-apoptotic genes, Caspase-3, Caspase-2L and Bax. In contrast, IL-1β did not induce expression of pro-apoptotic genes, but it activated the expression of the short isoform of Caspase-2, Caspase-2S, eliciting anti-apoptotic effects (Fig. 1).

Table 1. *NF-κB binding activity (% of control)*

Antibody	Control	Glutamate	IL-1β
	100 ± 12	250 ± 22	230 ± 18
p50	20 ± 2	23 ± 3	15 ± 3
p65	51 ± 36	53 ± 5	93 ± 6
c-Rel	93 ± 11	248 ± 19	48 ± 7
p52	110 ± 5	208 ± 15	232 ± 23
RelB	98 ± 8	208 ± 17	229 ± 18

Densitometry analysis of the NF-κB complexes examined by EMSA and supershift analysis. The values of binding activity were expressed as a percent of the control value. Data are means ± S.E. of at least three experiments carried out in different rat granule cells preparations. * < 0.05 vs corresponding binding values obtained in the absence of an antibody. Data were analysed by Wilcoxon's rank sum test.

The IκBα inhibitor, BAY 11-7082, prevents NF-κB activation and neurotoxicity elicited by glutamate in rat cerebellar granule cells

We investigated the contribution of NF-κB activation to excitotoxic insult by studying the effect of an inhibitor of IκBα phosphorylation and degradation, the compound BAY 11-7082. In order to confirm the capability of BAY 11-7082, at 2 μM concentration, to down-regulate glutamate-mediated NFκB activation, we tested NFκB/DNA binding activity by EMSA technique. Nuclear extracts were prepared 45 min after glutamate and BAY 11-7082 treatments and then assayed for their DNA binding activity to the APPκB site. A representative experiment of gel shift analysis is shown in Fig. 2A. Glutamate significantly induced NFκB activity in neuronal cells (*lane 2*) when compared to BAY 11-7082 (*lane 3*). In particular, BAY 11-7082, applied during neurotoxic insult, inhibited the glutamate-induced up-regulation of NFκB binding activity (*lane 4*).

We then investigated whether NFκB activation was associated with prevention of glutamate toxicity. Cells exposed to 50 μM glutamate for 15 min, with or without 2 μM BAY 11-7082, were evaluated for their viability 24 hours later. As reported in Fig. 2B, the inhibitor of IκBα phosphorylation completely suppressed the glutamate toxicity, while per se, did not modify the cell survival.

Discussion

The functional significance of NF-κB activation in nervous cells is still not completely understood. A body of evidence indicates an opposite role for NF-κB

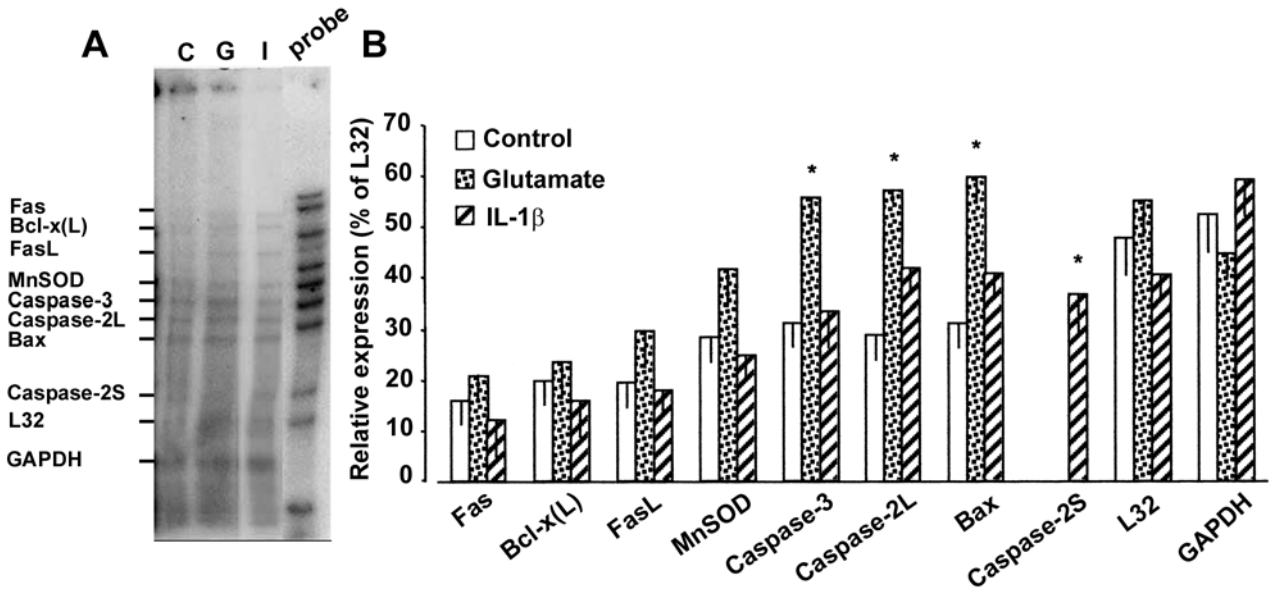

Fig. 1. (A) Representetative results of RPA analysis of Fas, Bcl-x(L), Fas-L, MnSOD, Caspase-3, Caspase-2L, Bax, Caspase-2S mRNAs in cerebellar granule cells exposed to glutamate or IL-1β. L32 and GAPDH mRNA was used to normalize the final results. (B) Densitometry analysis of glutamate- and IL-1β-induced gene expression (* $p < 0.05$ vs control value)

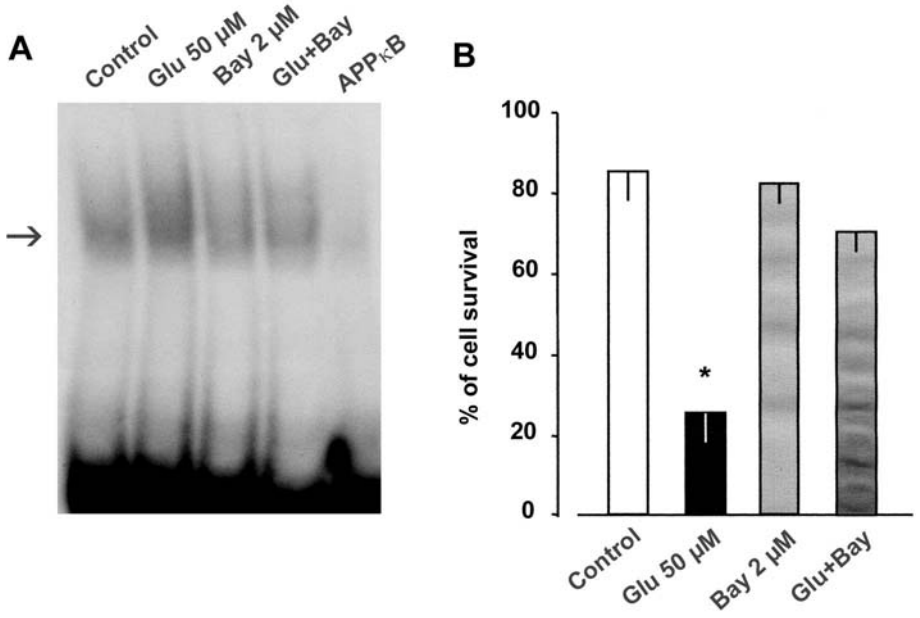

Fig. 2. (A) Effect of BAY 11-7082 on APP-κB binding activity elicited by glutamate in rat cerebellar granule cells. This picture shows NF-κB activation in cells untreated (*lane 1*), treated with glutamate (*lane 2*), treated with BAY 11-7082 (*lane 3*) and glutamate plus BAY 11-7082 (*lane 4*). (B) Effect of BAY 11-7082 on glutamate-induced neurotoxicity in rat cerebellar granule cells (* $p < 0.01$ vs control value). Neurotoxicity was measured as previously reported [18]

proteins in the regulation of cell survival. By targeting diverse NF-κB subunits, through application of antisense oligonucleotides to primary neuronal cultures, or using c-Rel knockout mice, we showed that different NF-κB factors can be involved in the regulation of cell death and survival. The glutamate-induced neurotoxicity is dependent on p50/p65 activation, while IL-1β neuroprotection relies on c-Rel activation [18]. These results suggested that cell response to NF-κB activation may depends, beside the cell phenotype, on

the specific composition of NF-κB dimers activated by external stimuli.

In this study, we show that the activation of different NF-κB factors by glutamate and IL-1β is also associated with opposite regulation of genes involved in the control of apoptotic program. Administration of glutamate in rat cerebellar cultures induced the expression of pro-apoptotic genes Bax, Caspase-3 and Caspase-2L [5]. IL-1β did not activated pro-apoptotic genes, but it induced the expression of the anti-apoptotic protein Caspase-2S [23]. These genes are known to be key regulators of apoptotic cell death. In different cell models of apoptosis, Bax, a member of Bcl-2 family, was found to translocate from the cytosol to mitochondrial membranes, where it oligomerizes and facilitates mitochondrial membrane permeabilization [7]. Caspases belong to the family of cysteine proteases, and have a central role in facilitating a number of morphological and biochemical changes during the programmed cell death. Activation of Caspase-3 was found to precede neuronal death in a rat model of transient focal ischemia, where caspase-3-dependent deoxyribonuclease activity caused internucleosomal DNA fragmentation [12]. Caspase-2 is a long prodomain containing enzyme that is activated in response to various apoptotic stimuli in many cell types. It has been reported the existence of two isoforms of Caspase-2 in brain: a short form, Caspase-2S, and a longer form, Caspase-2L. Overexpression of Caspase-2L induces programmed cell death in Rat-1 cells. Conversely, overexpression of the Caspase-2S suppresses Rat-1 cell death induced by serum deprivation [23]. This suggests that Caspase-2 plays an important role in both positive and negative regulation of programmed cell death.

We also studied the effect of NF-κB inhibition on neuron viability. The activation of NF-κB results from IκB phosphorylation, operated by a protein kinase complex, and subsequent IκB degradation. Glutamate-induced cell death was found to be prevented by administration of aspirin and sodium salicylate [6], which by inhibiting IκB phosphorylation prevent NF-κB activation and nuclear translocation [10]. A recently identified inhibitor of IκBα phosphorilation, namely BAY 11-7082, was demonstrated to have a potent anti-inflammatory action in edema and in a rat arthritis model [16]. Moreover, addition of this drug to neoplastic multiple myeloma cells suppressed the NF-κB/DNA binding activity and induced apoptosis [4]. We tested the effect of BAY 11-7082 on glutamate toxicity. Our results indicate that, at a concentration inhibiting NFκB activation, BAY 11-7082 was able to revert glutamate-induced cell death.

These data give additional evidence about the detrimental role of NFκB p50/p65 activation in glutamate toxicity. In particular, the neuroprotective effect of BAY 11-7082 strongly indicates that inhibition of IκBα phosphorylation may represent a suitable strategy for a wide therapeutic intervention covering, besides inflammatory and neoplastic diseases, also neurodegenerative disorders associated with brain injury.

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Reorganization of cerebral circuits in human brain lesion

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Summary

Recovery after focal brain lesions is supposed to be mediated by cerebral reorganization. Stroke is a powerful model to study these processes in the human brain, since middle cerebral artery infarction is a common neurological disease with a clearly defined onset of a lateralized sensorimotor deficit syndrome. Brain tumours constitute a further model differing from stroke by their slow lesion dynamics. Evidence from functional neuroimaging and transcranial magnetic stimulation will be presented showing that recovery of hand function is related to reorganization of local perilesional and large-scale circuits involving the contralesional hemisphere.

Keywords: Cerebral plasticity; neurorehabilitation brain injury.

Introduction

Since the pioneering work of Merzenich and his colleagues [22] it is known that reorganization can take place in the adult nervous system. Both, overuse and disuse of limbs were shown to lead to an increase or decrease of the corresponding representations in the cerebral cortex, respectively. The pivotal question for restorative neurology is whether such plasticity also operates after cortical damage. Ablation of the hand area in somatosensory cortex of the monkey (SI) has been shown to lead to an immediate unresponsiveness of the hand representation in SII, the second somatosensory cortex, a functionally related but distinct cooperative area [26]. Twenty-four hours later the unresponsive hand area in SII was occupied by a foot representation indicating lesion-induced plasticity. Further, Nudo *et al.* [25] observed that the motor cortical finger representations adjacent to partly damaged finger representations became enlarged in relation to rehabilitative treatment, while they remained unchanged in the monkeys not subjected to rehabilitative treatment. In such experiments evidence was provided showing that reorganization occurs in the adult nervous system both adjacent to a focal brain damage leading to plastic changes of the representation within the affected system as well as remote from the lesion in functionally related systems [36]. Here we review recent work on cerebral reorganization after lesions of the motor system obtained with non-invasive neuroimaging methods. We will focus on representational plasticity and reorganization of neural networks beyond the perilesional area.

Results and discussion

In human ischemic brain disease a sudden deprivation of blood supply due to arterial vessel occlusion induces an immediate cessation of brain function in the affected part of the brain. It is widely assumed that a larger ischemic brain lesion induces a more severe neurological impairment [23]. However, during the first hours after stroke onset, there is a dynamic evolution of processes culminating in the manifest infarct lesion. As was shown by magnetic resonance imaging (MRI), the area with impaired blood supply as evident from perfusion imaging (PWI) is usually larger than the area of structural tissue damage as assessed with diffusion weigthed imaging (DWI). This so-called PWI-DWI mismatch area signifies the brain tissue at risk of infarction (Fig. 1). In fact, thrombolysis was shown to restore cerebral blood flow by early recanalization of the occluded cerebral artery which is suited to salvage a large portion of the ischemic brain tissue [12, 14, 28, 33]. Figure 1 shows the results of a quantitative volumetric study in acute stroke patients. It becomes clear that in the patients subjected to thrombolysis the manifest ischemic brain lesions as assessed

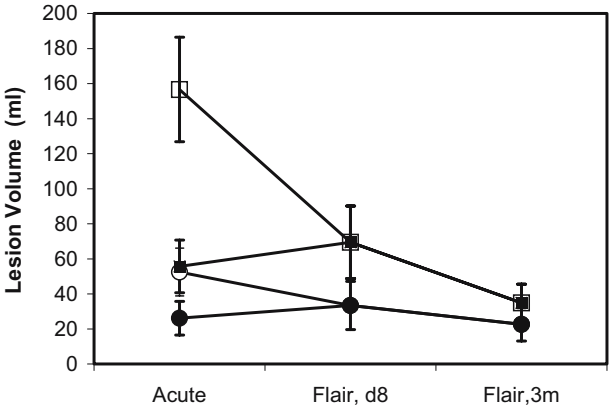


Fig. 1. Lesion evolution in middle cerebral artery infarction. Severe perfusion-diffusion mismatch in the patients subjected to intravenous thrombolysis (squares) and minor perfusion-diffusion mismatch in patients not eligible for thrombolysis (dots). Note the prediction of the infarct lesion on day 8 by the lesion in diffusion weighted imaging in the acute stage (filled symbols) and lesion regression in the subsequent months. Open symbols show lesion volumes as assessed in perfusion weighted imaging in the acute stage

in MRI on day 8 were predicted by the acute DWI-lesions, while the infarct lesions shrink thereafter as evident from follow-up measurements 4 months after stroke [15]. It is important to realize, however, that the PWI-DWI mismatch is not a stable phenomenon. It is particularly severe in proximal cerebral artery occlusion due to viable leptomeningeal collaterals while there is virtually no PWI-DWI mismatch in distal cerebral artery occlusion including lacunar strokes [8, 28]. Furthermore, since the PWI-lesion signifies the brain tissue at risk of infarction, the PWI-DWI-mismatch declines with increasing intervals from stroke onset due to a secondary growth of the DWI lesion [33]. Both of these factors account for the virtually identical magnitude of the PWI- and DWI-lesions in the patients who were not eligible for thrombolytic stroke therapy (Figure 1). It is interesting to note that the residual brain lesions in the patients subjected to thrombolysis were approximately as large as the lesions in the non-treated control patients. This was reflected by a similar neurological impairment in the two patient groups four months after stroke, whilst the patients subjected to thrombolysis were far more severely affected in the acute stage of stroke. Note that patients with a manifest brain infarct as large as the PWI-lesions in the patients eligible for thrombolysis (Figure 1) were shown to fail to recover altogether [1, 2].

One of the most critical issues related to post-stroke recovery is the question which portion of brain tissue mediates recovery. Specifically, can the perilesional tissue take over or regain functional activity after ischemic damage of the original representation? Alternatively, does the contralesional hemisphere enable functional recovery? Both factors have been discussed extensively in the literature [4, 27, 32]. We will provide evidence by functional magnetic resonance imaging (fMRI) that the perilesional cortex is of fundamental importance. Figure 2 shows the results of multimodal image integration in a patient suffering from acute right hemispheric stroke. The severe hemiparesis was due to a large area of severe hypoperfusion as evident from PWI, while the structural brain lesion as evident from DWI was relatively small. Due to rapid recanalization leading to restoration of brain perfusion the resulting infarct did not exceed the acute DWI-lesion. The hemiparetic patient was subjected to rehabilitative training and recovered virtually completely that she could execute sequential finger movements of the formerly affected hand again. FMRI showed activation of the sensorimotor cortex and abnormally strong activation of the supplementary motor area in the frontal midline, a pattern typical for sequential finger movements [21, 31]. Notably, however, the activation of the sensorimotor cortex occurred within the former area of impaired perfusion immediately adjacent to the infarct lesion in motor cortex (Fig. 2). Further, movement-related activity was restricted to the affected and active hemisphere reflecting successful recovery [7, 9, 21]. Both aspects suggest that recovery was mediated by recuperation of function in the perilesional cortex by local remapping of local circuits as a consequence of the infarct lesion within motor cortex. Transcranial magnetic stimulation (TMS) has provided supplementary information showing that the initial paresis after stroke may in part be related to perilesional exaggerated inhibition [6].

A local remapping of function adjacent to a brain lesion was demonstrated previously in slowly growing brain tumours [30]. In fact, lesion morphometry revealed that the shift of the functional representation was determined by the location of the tumour within the brain: dorsally located gliomas induced a ventral displacement of the motor hand area, while ventrally located gliomas induced a dorsal displacement of the motor hand area with progressive loss of function in proportion to tumor growth [37]. FMRI allows a more detailed analysis of such changes due to the favourable signal-to-noise ratio and spatial image resolution [16].

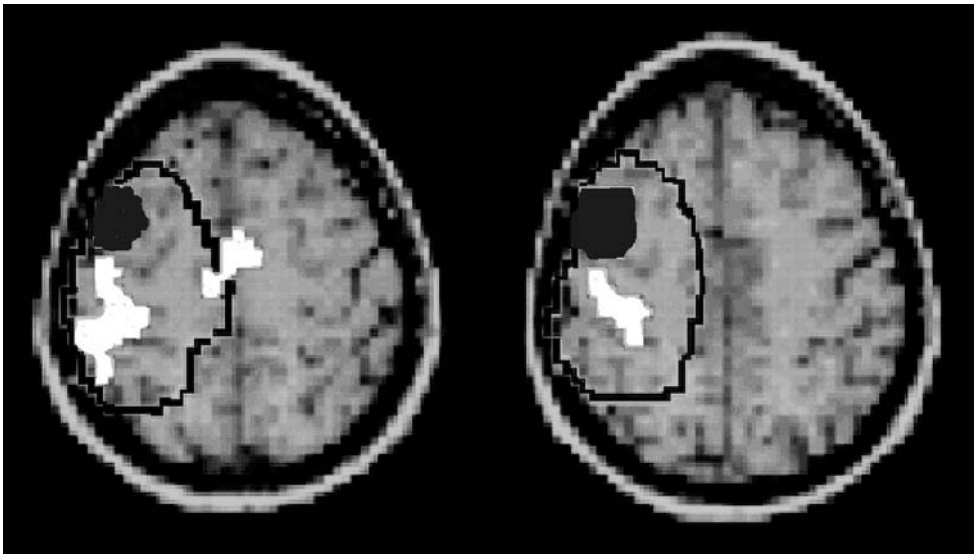
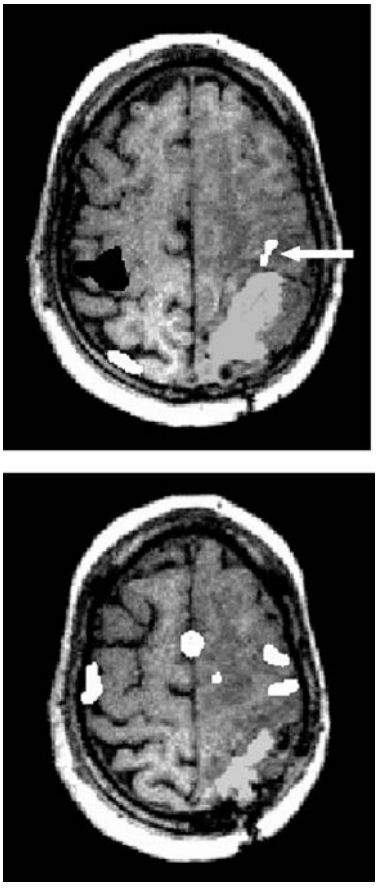


Fig. 2. Activation related to finger movement activity adjacent to the infarct lesion (dark grey area) after complete recovery from hemiplegic stroke. The activation areas ($p < 0.01$ corrected) mapped to the sensorimotor cortex and the supplementary motor area occurred within the area of severe hypoperfusion in the acute stage of stroke (outlined in black)



As an example a patient is described who had become symptomatic with epileptic seizures due to a large isomorphic glioma in the left parietal lobe with diffuse infiltration of the frontal lobe (Fig. 3). The patient presented with slightly slowed finger movements of his right hand accompanied by elevated muscle tendon reflexes on his right side. Finger movement activity with the right hand resulted in a dorsal shift of the activation area in the left sensorimotor cortex which amounted to 13 mm as compared with the activation area related to finger movements of the normal left hand. Note in addition, that during finger movements with the contralesional hand abnormal activation areas occurred also in the non-affected hemisphere. These abnormal activations suggest deficit compensation employing functional representations of the contralesional hemisphere as will be discussed below. Unexpectedly, however, direct comparison of the two

Fig. 3. Activation related to finger movements in a patient suffering from a left hemispheric glioma. Right finger movements elicited abnormal activation areas (white areas) in a dorsally displaced location as compared with the hand representation in the non-affected hemisphere activated by left finger movements (black area). However, the direct comparison of the activation patterns related to finger movements of either hand showed a significant activation in the depth of the central sulcus at a virtually normal position in relation to finger movements of the contralesional hand (arrow)

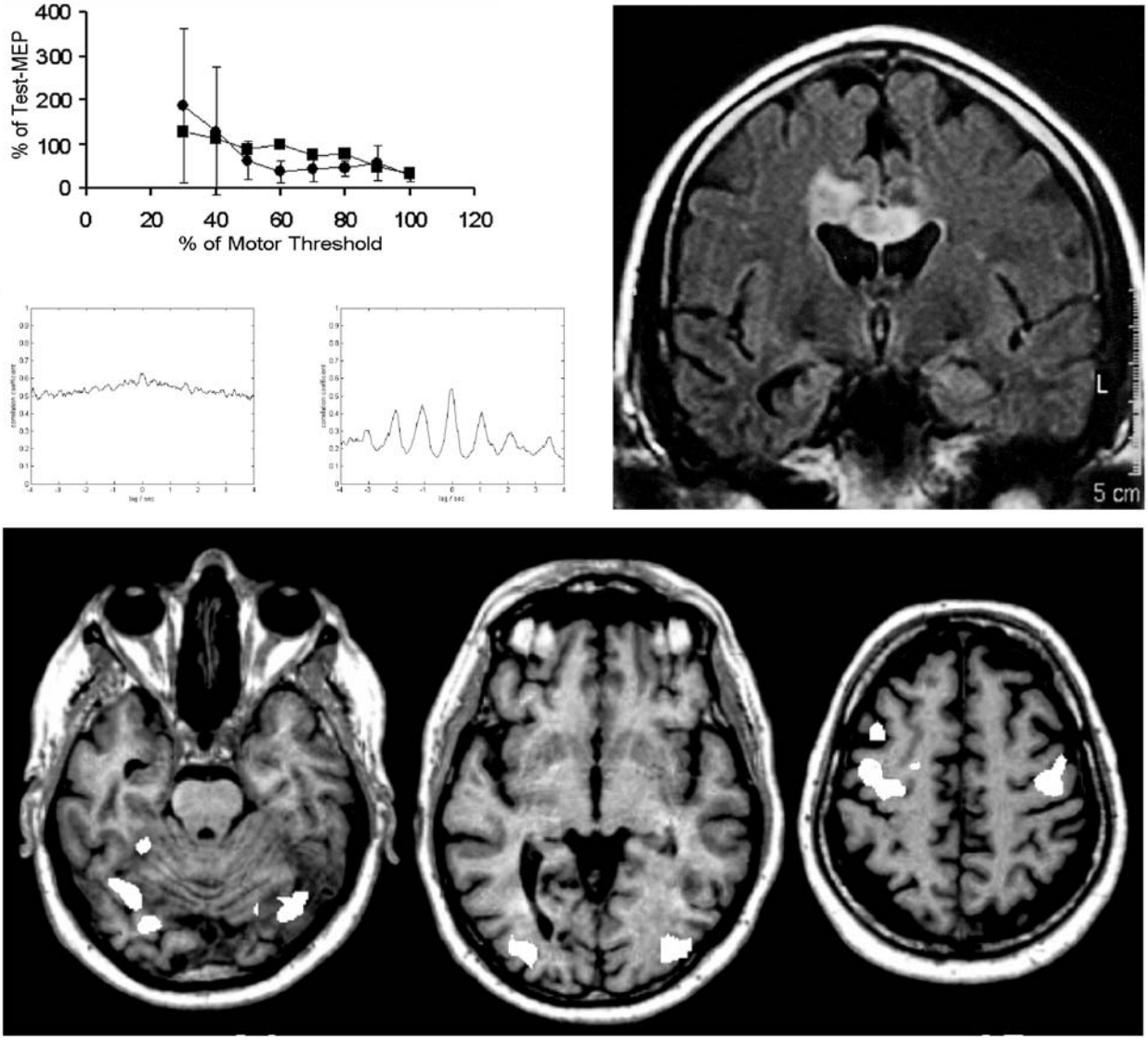


Fig. 4. Synchronization of finger movements by visual pacing in a patient with a severe bimanual coordination deficit resulting from a complete infarction of the corpus callosum. The dissociation of the bimanual finger movements was not accompanied by a disinhibition of the motor cortex as evident from the normal inhibition curves obtained with paired-pulse transcranial magnetic stimulation at increasing strength of the conditioning stimulus. Note the good autocorrelation of electromyographic activity of both hands in visually guided bimanual finger movements in contrast to the lack of autocorrelation in self-paced bimanual finger movements. Visual guidance of bimanual finger movements activated a bilateral circuit involving the visual association cortex, the dorsal premotor cortex and the anterior cerebellum

activation patterns revealed an area of enhanced activity related to finger movements of the right hand deep in the compressed left precentral gyrus at a virtually normal position. Thus, one might argue that this spot of activity was possibly the crucial area maintaining hand function in this patient. Alternatively, finger movements in the ipsilesional hand may inhibit transcallosally the motor cortex in the affected hemisphere which is the case in the normal brain as evidenced by TMS techniques [3, 19, 20, 34].

Transcallosal inhibition is impaired in the contralesional motor cortex in patients who recover from middle cerebral artery infarction [3, 34]. As a functional counterpart such patients show abnormally enhanced activity related to finger movements with the affected hand in premotor and motor cortex of the ipsilateral unaffected hemisphere [7, 21, 31]. In fact, interference experiments with TMS provided evidence that the premotor cortex in the non-affected hemisphere plays a crucial role in post-stroke recovery [13].

Similarly, glioma patients may show enhanced activity in the premotor and motor cortex of the contralesional hemisphere (16, 30, Figure 3) corresponding to the findings in stroke patients. Such data are suited to substantiate the hypothesis that the non-affected cerebral hemisphere supports the affected crebral hemisphere in a plastic fashion. This may happen in stroke recovery, during ongoing compensation of a progressive loss of function due to a neoplastic or degenerative brain disease, or in relation to an alternative strategy of behaviour ensuing brain damage [11].

The transcallosal communication of the two cerebral hemispheres is of great importance for a large number of daily activities involving both hands. In most manual activities, the dominant hand interacts with an object, while the opposite hand stabalizes it. Thus, there is a continuous exchange of sensorimotor information between the two cerebral hemispheres. If this communication is disturbed, bimanual coordination deficits can be expected. Indeed, we recently observed a patient with a severe bimanual coordination deficit resulting from an infarction of the entire corpus callosum (Fig. 4). The patient presented with focal motor seizures. He was unable to turn the pages of a newspaper or to cut meat on his plate, since he could not release the grip of one hand, and was unable to move the fingers of his hands synchronously. However, when provided with a visual cue he succeeded in synchronizing his finger movements. This external pacing of the two motor systems in his right and left hemispheres was accompanied by a bilateral activation of his dorsal premotor cortex, visual association cortex and anterior cerebellum. Notably, there was no disinhibition of motor cortex on either side (Fig. 4) which is the case in patients with infarcts involving the sensorimotor cortex [3, 19, 20, 34]. This suggests that cortical disinhibition is not the result of a transcallosal disconnection but rather the consequence of a lesion induced imbalance of cortical excitability and inhibition reflecting the different excitation thresholds of excitatory and inhibitory neurons [5, 24, 29].

In conclusion, recovery of motor functions after focal brain lesions relies critically on reorganization of local circuits in the affected cortex and, in addition, is subserved by large-scale reorganization involving the homologue areas of the contralesional intact cerebral hemisphere. Note, that the cortical activations are densely connected with subcortical relay nodes in the basal ganglia and cerebellum which also have been implicated for recovery [35]. Cerebral reorganization can probably be enhanced by dedicated training [10, 17, 18] and is supposed to be working also in postlesional recovery of language and cognitive functions which is being investigated in our laboratory.

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Transcranial magnetic stimulation in neurorehabilitation

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Summary

In neurorehabilitation, transcranial magnetic stimulation (TMS) offers information regarding prognosis and pathophysiology and could also be useful for therapeutic purposes. Numerous studies have indicated that, after stroke, the absence of motor evoked potentials is associated with a poor motor recovery. In contrast, MEPs obtained in the paretic muscle with low stimulus intensities suggest a good restitution of motor function. TMS studies have shown that the location of a brain lesion determines motor cortex excitability changes: Patients with central somatosensory lesions show a disinhibition in the ipsilesional motor cortex. Lesions in the territory of the superior cerebellar artery are associated with a loss of motor cortex excitability. Stroke patients participating in a Constraint-induced movement therapy show an enlargement of the motor output area in the affected hemisphere after therapy. This enhancement of motor excitability is associated with an improvement of motor function. Some evidence is emerging that the application of low frequency repetitive TMS over the non-lesioned hemisphere improves neglect phenomena by down-regulation of the excitability of the non-lesioned hemisphere.

Keywords: Transcranial magnetic stimulation; stroke; intracortical inhibition; constraint-induced movement therapy.

Introduction

In 1985, transcranial magnetic stimulation (TMS) was introduced by Barker *et al.* [1]. This technique allows to investigate the integrity of the central motor pathways by a painless stimulation of the motor cortex. Some information about motor excitability is provided by determination of the motor threshold (MT). MT is the stimulator output intensity that evokes motor potentials with an amplitude > 50 μV [18]. Within the last 12 years, additional techniques have been developed to explore motor cortex excitability in greater detail. One of them is mapping of the motor output area of a target muscle by using a focal (figure-of-eight) coil [24]. Various conditions have been shown to modify such a cortical representation area, e.g. immobilization reduces the map size [15] and motor learning enlarges the output area [17]. Another technique is the application of paired pulse TMS in which a first, conditioning pulse with an intensity below the motor threshold is followed by a suprathreshold (test) pulse [8]. Depending on the interval between both stimuli, this paradigm tests Intracortical Inhibition (ICI) or Intracortical Facilitation (ICF). Typically, ICI is produced with interstimulus intervals of 1–4 msec, ICF occurs with intervals of 6–20 msec. It has been shown repeatedly that ICI and ICF are phenomena in the motor cortex.

With repetitive TMS it is possible to modulate the excitability of the brain not only during the application of the stimuli but also for up to several hours afterwards. In healthy subjects, low frequencies (1 Hz) produce a down-regulation of excitability and high-frequency stimulation (e.g., 5 Hz) induces increases of excitability (for review: 20).

In this paper I will present several TMS studies dealing with prognostic, pathophysiological and therapeutical aspects.

TMS as a prognostic tool

In numerous studies TMS has been used as a predictor of outcome after stroke. Several papers have identified the MT as a sensitive prognostic parameter: the higher the MT the poorer the motor recovery (for review: 9). Some studies repeated TMS to compare electrophysiological follow up with clinical progress [9].

A majority of studies supports the following statements:

1. Patients in whom MEPs can be elicited in the paretic limb early after stroke have a significantly

better clinical outcome than patients without MEPs at early stage.
2. Presence or absence of a MEP is a more important variable than a differentiation between normal and delayed central motor conduction times (CMCT).
3. TMS should not only be performed while the target muscle is relaxed but also during facilitation (contraction of the target muscle or, if impossible, innervation of the homologous contralateral muscle). Patients without MEPs at rest but with MEPs during facilitation have a substantially better prognosis than patients who have no MEPs during facilitation.
4. The inability to obtain MEPs early after stroke is associated with a poor recovery.
5. Motor thresholds are often elevated after stroke (particularly in subcortical strokes). They tend to decrease in the subsequent months. The best predictive value was found when determining motor threshold 30 days after stroke but even threshold evaluation within the first 8–24 hours after stroke may predict outcome.

TMS for studies of pathophysiology

After a stroke, Intracortical Inhibition is decreased, suggesting an enhancement of motor cortex excitability. This phenomenon has been found in the affected hemisphere [5, 14, 16] but also the non-lesioned hemisphere [3, 12, 19]. Currently the relevance of these findings regarding motor recovery is unclear: in the study by Bütefisch *et al.* [3] the increase of intracortical excitability in the non-lesioned hemisphere was only seen in patients with good recovery but not in those with poor recovery. In contrast, Manganotti *et al.* [16] described normal intracortical excitability in the non-lesioned hemisphere of stroke patients with significant motor recovery, and Shimizu *et al.* [19] found intracortical disinhibition of the non-lesioned hemisphere in patients with poor motor recovery.

Recently we have gathered evidence that lesions in central somatosensory systems also affect motor cortex excitability: A patient with a vascular lesion in his primary somatosensory cortex had a loss of ICI and an increase of ICF in the lesioned hemisphere [11]. Similarily, patients with a hemihypesthesia due to a thalamic infarction also showed a loss of ICI in the affected hemisphere [13]. These results suggest that, under normal conditions, the central sensory system exerts an inhibitory influence on the motor cortex.

In contrast, patients with an infarction in the territory of the superior cerebellar artery show an increase of ICI and a loss of ICF in the corresponding motor cortex (Liepert *et al.*, unpublished observations). This result indicates that, under normal conditions, the cerebellum has a facilitatory influence on motor cortex excitability.

A rather consistent finding across studies is that, after a stroke, the motor output map of the paretic muscles is decreased in comparison with the healthy side, suggesting a reduced corticospinal excitability in the lesioned hemisphere [4, 10, 22, 25]. During subsequent months motor output areas in the affected hemisphere enlarge. This change is associated with an improvement of motor functions.

We used TMS mapping to study the effects of a specific physiotherapeutic intervention in stroke patients in the chronic stage of their illness (stroke more than 6 months ago) [9]. Patients were tested two times prior to the intervention (baseline measurements, 2 weeks apart) and then 1 day, four weeks and 6 months after the intervention. The treatment is called Constraint-induced movement therapy [21] (CIMT). The treatment period was 12 days. During this time patients had their *unaffected* arm immobilized in a sling for 90% of waking hours. They received intense training for the affected arm (6 hours/day). The baseline measurements showed a smaller motor output map in the affected hemisphere. This representation area was significantly enlarged after therapy and gradually decreased to some degree during the subsequent 6 months (Fig. 1). In parallel, motor functions as measured by the motor activity log improved. We found a significant shift of the center of gravity of the ipsilesional motor output map after therapy. Our conclusions from this study were as follows:

1. Even chronic stroke patients benefit from CIMT. The improvement of motor functions lasts for at least 6 months.
2. CIMT induced a strong increase of motor excitability in the affected hemisphere. The gradual reduction of excitability over the subsequent months presumably indicates an enhanced synaptic efficacy since motor performance remained stable.
3. The shifts of the centers of gravity of the motor output map in the lesioned hemisphere suggest that, after therapy, additional brain areas had been recruited. This would indicate a ''true'' reorganization of the brain.

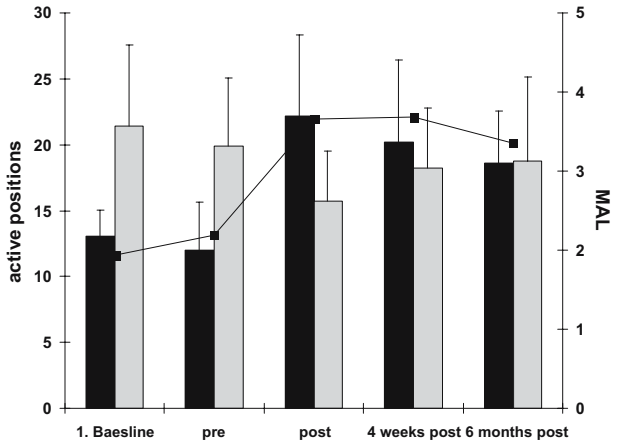

Fig. 1. Number of active TMS positions in the infarcted (black bars) and non-infarcted (grey bars) hemispheres two weeks and one day pre-treatment and 1 day, 4 weeks and 6 months post-treatment. Black squares indicate the corresponding motor activity log (MAL) data for the paretic limb, *: $p < 0.05$ (from: 9)

TMS to explore the functional relevance of brain areas

A transcranial magnetic pulse is able to disrupt the motor program for a short period of time. For example, reaction time is prolonged if the TMS pulse is applied close to movement onset. Johansen-Berg *et al.* [7] used such a paradigm to study the functional relevance of the contralesional premotor cortex in patients with stroke. They found that reaction time prolongations only occurred in stroke patients but not in normal subjects, suggesting that the contralesional premotor cortex was relevant for motor execution in the stroke patients.

TMS as a therapeutic tool

Since repetitive TMS (rTMS) is able to modulate brain excitability, this technique was applied in various patient groups in order to improve their motor performance. In some studies rTMS was temporarily able to reduce symptoms in Parkinson's disease (for review: 23) and focal dystonia (for review: 6). Brighina *et al.* [2] applied rTMS in 3 patients with neglect phenomena due to a stroke. They hypothesized that the non-lesioned hemisphere might exert an unfavourable influence on the lesioned hemisphere, thus further impairing the function of the affected hemisphere. They used 1 Hz rTMS to down-regulate the excitability in the non-lesioned hemisphere and described an impressive reduction of neglect symptoms.

In summary, TMS is a useful tool not only to explore motor cortex excitability and corticospinal tract functions but also to study the functional relevance of distinct brain areas. In the future, it might also serve as a therapeutic tool.

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Is there impairment of a specific frontal lobe circuit in head injury?

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Summary

There has been considerable interest in the role of anterior cingulate and lateral frontal cortex in normal cognition, and particularly its role in cognitive control. It has also been suggested that dysfunction of this frontal brain circuit is responsible for many of the cognitive deficits observed after head injury. Several recent PET and SPECT studies of head injury have lent support to this idea, and suggest that the hypothesis is worth further examination. The paper presents a selective overview of evidence that this specific frontal lobe circuit is impaired after head injury.

Keywords: Head injury; frontal lobes; cognition.

Over the past decade there has been intense interest in the role of anterior cingulate cortex (ACC) and lateral frontal areas in normal cognition, spurred by PET and fMRI studies demonstrating activation in these areas in a wide variety of cognitive tasks [4]. One influential view of the role of the anterior cingulate is that it forms a key part of a system for executive attention [8]. Although it is generally believed that anterior cingulate is involved in cognitive control, the literature indicates diverse roles and there is as yet no unifying account of the functions of ACC [3]. The potential relevance of this frontal brain circuit to head injury was pointed out by Azouvi [1] who concluded that "... the main cognitive and behavioural deficits of severe TBI patients are related to a defective activation of an anterior attentional/executive network, including the prefrontal cortex and the cingulate gyrus". The aim here is to give a brief overview of evidence for the hypothesis that damage to a specific frontal network is one of the key impairments in head injury.

The view that frontal functions are compromised in head injury is popular and well established, and indeed patients are often described in a clinical context as having "frontal behaviour" or "executive difficulties". The case for the importance of frontal dysfunction was eloquently made by Walsh [11] among others [7]. Walsh [11] provides a wide-ranging review of the consequences of head injury focussing on adaptive behaviour and problems related to frontal lesions. He refers to the tripartite distinction between dorsolateral, medial, and baso-medial frontal areas, and outlines various neuropsychological deficits that he links to each of these areas. On this classic view damage to dorsolateral frontal cortex is related to impairments of planning and learning, conceptual behaviour, mental set and perseveration, complex integration and problem solving; damage to basomedial cortex is related to disinhibition and personality change; and damage to the medial cortex is related to adynamia. In head injury Walsh [11] ascribes greater importance to damage to lateral frontal and orbito-frontal regions than medial frontal damage. This is reasonable because the structural effects of traumatic brain injury are often most obvious in orbito-frontal and lateral frontal regions, and Walsh [11] repeats conventional wisdom that medial frontal cortex is "less often damaged" in head injury.

Yount *et al.* [12] conducted a study which illustrates the difficulty of demonstrating structural abnormality in medio frontal regions. They analysed MR images from 27 TBI cases and compared them with 12 controls drawn from a normative database. They found evidence of atrophy of the posterior cingulate gyrus, thalamus and corpus callosum. Although there was no difference overall between patients and controls in the anterior cingulate, patients with moderate and severe TBI had atrophy of the anterior cingulate in comparison to patients with mild injuries. Yount and colleagues [12] make an interesting and salutary point concerning the problem of measuring the anterior cin-

gulate: some people have a single gyrus and others have two parallel gyri. People with the latter morphology naturally tend to have a larger anterior cingulate surface area. Such gross pre-existing individual differences in cingulate morphology will clearly make it difficult to establish post-traumatic relationships. Thus, measurements of cingulate surface area may be relatively insensitive to atrophy and change in functional integrity.

Conventional wisdom that medial frontal areas are typically spared in head injury is strongly challenged by functional imaging studies. Stamatakis *et al.* [9] describe a SPECT blood flow study of 61 patients with head injury who had been admitted to a neurosurgical unit. Acute and follow-up HMPAO SPECT images of head injured patients were individually compared with 32 normal controls using Statistical Parametric Mapping (SPM). Composite images were constructed showing areas with the most frequent blood flow abnormalities. As expected abnormalities in temporal and lateral frontal areas were common, but, strikingly, so also were blood flow abnormalities in medial frontal cortex including the anterior cingulate. Abnormalities in medial frontal areas were observed in patients with both focal and diffuse injury classified using MR, suggesting that dysfunction in mesiofrontal cortex is common after both types of structural damage.

Evidence that dysfunction in the anterior cingulate plays a role in deficits after head injury also comes from functional imaging studies [2, 5, 10]. Fontaine and colleagues [5] carried out PET imaging of resting metabolic activity in 13 patients with severe TBI without focal lesions. On a region of interest analysis they found robust correlations between performance on cognitive tests and metabolism in prefrontal and cingulate cortex, but not other regions such as temporal or occipital cortex. Significant correlations were mainly with left hemisphere regions for verbal tasks, and more bilaterally for visual memory. Interestingly significant correlations were found for tests of memory as well as tests of executive and attentional functions. These authors conclude that head injury patients have dysfunction in an anterior attentional network, thus explaining their problems in memory, attention, and executive functions. An analysis of SPECT images by Stamatakis *et al.* [10] showed a relationship between performance on the Rey Figure task and prefrontal and medial frontal regions, including the anterior cingulate.

Further evidence for functional changes in the anterior cingulate after head injury comes from an activation study by Levine and colleagues [6]. They carried out a PET $H_2\ ^{15}O$ activation study (an rCBF method) in 6 moderate or severe TBI patients with good recovery and 11 healthy controls. Participants performed a paired associate learning task, and activation was studied during the retrieval phase. Patients showed greater activation than healthy controls, and recruited additional areas: anterior cingulate showed significantly greater activation in patients than controls; patients also showed more bilateral activation.

The results of the study by Levine and colleagues [6] demonstrates that there is an abnormal response to task demands after head injury, which is evident in anterior cingulate and other regions. The result is intriguing, but like any activation study in a brain damaged group it is difficult to interpret. The response may be part of an adaptive process of compensation for inefficient memory processes, in which patients recruit a wider network of areas to compensate for the reduced efficiency of their memory processes. Alternatively the result may indicate abnormal function in the frontal lobe. These explanations are not mutually exclusive, and other evidence suggests that both may be true. The functional imaging studies considered above [5, 9] show that ACC may often be abnormal in the resting state. It is also well established that ACC is activated when cognitive tasks require increasing effort [4]. We can speculate that the study by Levine and colleagues [6] shows compensation by a brain circuit that is itself dysfunctional. This idea is in line with classic views such as that of Walsh [11], that one of the key problems for people with head injury is that frontal mechanisms for compensation and adaptation are impaired while at the same time there is a greater demand on such mechanisms.

Evidence that a specific frontal network is impaired in head injury is supportive and intriguing but is currently inconclusive. To date the most convincing evidence for a link comes from studies employing functional imaging. In the past studies of head injury using brain regions of interest have tended to overlook the ACC as a separate area, and this region should come under more specific study in the future. It is particularly exciting that there is the possibility of making a link between activation studies in normal volunteers, and the impairments observed after brain injury. The extensive literature on activation of these frontal regions in normal volunteers suggests that dysfunction of this circuit may account for emotional and social

problems seen after head injury, as well as cognitive deficits extending beyond those that are classically thought to reflect ''frontal'' or ''executive'' deficits.

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Treating the aging brain: cortical reorganization and behavior

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Summary

Aging comprises many physiological modifications, including structural and metabolic changes, yet little is known about how aging affects the way in which neurons process and integrate sensory information from the environments. Here the framework of "modified use" as a determinant of cortical reorganization was applied for the investigation of age-related modifications of cortical maps and processing, and of associated changes of behavior. The age-related changes of walking behavior in rats were contrasted with the parallel changes of sensorimotor processing developing at the cortical level. Based on the regional specificity of these changes attempts are made to separate age-related changes arising as a consequence of degeneration from a result of adaptable processes following reduced use at high age. Finally, findings from long-term treatment with the Ca^{2+}-blocker nimodipine, or from housing animals under enriched environmental conditions to ameliorate aging effects were described. Combined, these results show the general treatability of age-related changes. The data imply that age-related changes can be reversed by short periods of training and stimulation schedules even if they have developed. Clearly, the development of specific measures to delay aging processes and to rehabilitate aged brains depends on future progress in understanding mechanisms and effects of aging.

Keywords: Degeneration; plasticity; walking behavior; sensorimotor performance; enriched environment; training; cortical maps; reorganization; rats; nimodipine.

The aging brain: socio-political background

We witness a unique restructuring of the aging pattern in the societies of the industrial nations, characterized by an increasing probability to reach high age. Concomitantly, the probability to suffer from age-related disorders is raised dramatically, indicating an urgent need for increasing efforts towards a more comprehensive understanding of the different facets of aging. Therefore, the investigation of the aging brain is not only fascinating from the standpoint of how aging affects neural structures, but vital with respect to the innumerous implications for a wide range of social disciplines such as psychology, sociology, health care, and politics in general [1, 25].

Given this scenario, the preservation of every-day life competence of aged populations becomes increasingly important. In particular, the maintenance of sensorimotor abilities is a crucial prerequisite to be able to live largely independent. In this context it is of far-reaching consequences, whether age-related changes are due to the accumulation of degenerative processes and are by that largely irreversible, or whether age-related changes reflect plastic adaptations, and therefore allow for effective treatment [5, 6, 15, 23].

From the very beginning of human civilization, the process of aging appeared to exert a peculiar attraction and fascination. The fear of aging, and the associated inevitable vanishing of life quality, finds its expression in a desire for measures that provide longevity, a yearning frequently captured in fine arts. However, it is only for a few decades that we experience a dramatic increase of life span. Although growing old is an old problem, the emergence of such a longevity for a substantial portion of the population is a fairly new phenomenon.

Aging theories

In search of an understanding of normal, not pathological aging processes, a number of "aging theories" have been developed. According to stochastic theories, aging processes are explained by a probabilistic accumulation of factors that progressively exert deteriorating effects onto the organism. On the other

hand, deterministic theories assume that aging is the consequence of endogeneous and/or genetically programmed processes. Among the stochastic theories are "tear and wear" [28], "free radicals" [16], "collagen/cross linkage" [44], "error and fidelity theory" [27] and the "immune theory" [45]. Deterministic theories are know as the "absolute metabolic scope theory" [36] and the "cell doubling theory" [17]. While each of these theories can account for some aspects observed during aging, there is now agreement that aging can not be explained by a single theory alone, but instead, that aging must almost certainly be regarded as caused by a multitude of factors.

Myths and facts

What do we know about the effect of aging on brain structures? "The concept that cortical neurons are lost with age and that this is the basis for cognitive decline is so embedded in our culture that when someone elderly is a little forgetful it is often said that 'He/she is losing his/her neurons'." (cited from ref. 30). In fact, the idea that there is a significant loss of neurons during normal aging dates back to Brody [2]. However, recent studies revealed an amazingly degree of stability in neuron number [11, 26, 30]. Besides technical problems associated with an accurate estimation of neuron numbers, a great problem lies in the enormous variation in neuronal numbers between individuals. For example, the size of area 17 in the human or primate brain can vary by a factor of three among individuals [30, 31, 42]. This huge variability raises doubt about the significance of a loss of up to 10%, when individual variations can be as much as 100% [30]. Similarly, a recent study by Rapp & Gallagher [34], who studied neuron numbers of representative samples of the entire hippocampus of behaviorally tested rats, reported no age-related loss of neurons, even from those animals with the greatest age-related behavioral impairments.

The question remains, are there then no structural counterpart to the clear impairment seen functionally during aging? It had been suggested that certain subpopulations of neurons might undergo a dramatic loss. Also, there can be a substantial reduction of specific sets of dendritic spines [31]. Molecular shifts in intact circuits have been described in the dentate gyrus of the monkey [13]. Aged rats with spatial learning deficits displayed significant reductions in synaptophysin immunoreactivity in CA3 relative to either young controls or age-matched animals with preserved learning [39]. Combined it appears now accepted that an age-related decline might be attributable to modifications at the subcellular level rather than cell numbers.

Aging of sensorimotor behavior and associated cortical maps

Aging comprises a number of physiological modifications, including structural and metabolic changes. While there is a growing body of information about age-related changes at cellular and biochemical levels, little is known about how aging affects the way in which neurons process and integrate sensory information from the environments. According to the concept of "use-dependent" plasticity, the young and the adult brain is in a state of permanent changes: Even small adjustments in every-day life routines that are accompanied by changes in behavior, can lead to major reorganizational processes [6]. Therefore, a prevailing question is how plastic processes affect aging processes. Here, we applied the framework of "modified use" as a determinant of cortical reorganization for the investigation of age-related modifications of cortical representational maps, response properties and associated behavior and perception [5, 6].

Rats are a convenient animal model as they age within 2 to 3 years. We therefore used aged rats to investigate the degree and the type of age-related changes at the level of sensorimotor cortical maps and processing by means of single cell recordings. To explore aspects of sensorimotor performance related to every-day life competence, we studied walking behavior. In old rats, the characteristic impairment of the sensorimotor state is most strikingly expressed in a walking impairment of the hindlimbs [15, 38, 41]. They show severe walking impairments – similar to old humans consisting of limping and dragging their hindlimbs (Fig. 1), while the forelimbs show little of these impairments [41].

Using electrophysiological recordings we demonstrated that the behavioral changes were paralleled by massive reorganizations of the somatosensory cortex such as an enlargement of receptive fields (RFs) of neurons of the cortical hindpaw representation, an increase of RF overlap and a deterioration of the topographic orderliness of the cortical maps (Fig. 2; refs. 6, 15, 41). In addition, temporal processing of the single neurons became impaired as indicated by a reduced capability to follow fast input sequences [6, 19].

In case of degeneration one would expect compa-

Fig. 1. Comparison of sensorimotor performance of young and of old rats. Footprints of the hindpaw as shown on the left are typically found in young rats serving as control group. This walking pattern is correlated with distinct and selective sensory inputs where single digits and pads are placed on the ground. Prints depicted in the middle and on the right are typical for old rats. The footprints shown in the middle are correlated with an intermediate state of sensorimotor performance; those on the right are correlated with multiple and diffuse inputs, sometimes even from the dorsal side of the paw; when the foot is twisted and dragged behind the body. (Reprinted from ref. 41; Lippincott Williams & Wilkins)

rable changes to occur in both the fore- and the hindpaw representation. However, analysis of RFs in the cortical forepaw representation of animals of high age revealed no alterations [15, 20]. At the same time, the sensorimotor behavior of the forelimbs remains largely unaffected even in animals of high age, presumably as a result of the maintenance of feeding and cleaning behavior. These results imply that age-related changes can be regionally very specific, and implicate a link between age-related neural changes and specific behavioral alterations emerging during aging. More generally, these findings extend the concept of use-dependent plasticity to high age (cf. 5, 6).

Perspectives for a treatment

It has always been a main concern to be able to interfere with aging processes in order to delay or to ameliorate the impact of age-related alterations. In rodents, it is well established that diet and caloric restrictions have a significant life-extending effect. There is a lively discussion about comparable effects on primates and humans [40, 46]. According to a longitudinal study using rhesus monkeys at the University of Wisconsin, the effects of caloric restrictions on longevity and diseases should be clearly seen by around 2020 [47]. On the other hand, there are many lines of evidence suggesting that maintained physical and mental exercise are prerequisites for what has been called "successful aging", although definite answers might revealed only in the next decades [10, 22].

Behavioral challenges through an enriched environment has been shown to exert beneficial effects on a wide range of morphological, molecular and physiologic features of the brain. Enriched environments, usually targeting sensorimotor modalities, have been shown to improve cognitive function [35], to facilitate recovery from injury or stroke [18] and to prevent age-related decrease in synaptic density in the aged brain [37]. When rats were housed under enriched conditions for their entire life beneficial effects on the development of age-related changes of cortical maps and RFs have been reported [4]. Even keeping aged rats under enriched environmental conditions for only a few months resulted in a significant amelioration of otherwise typical age-related alterations of sensory [3] and motor hindpaw representations [7]. These results indicate that the beneficial outcome of an enriched environment and thus the aspect of reinforced mobility and agility takes effect even in animals of high age. Comparable ameliorating effects on age-related changes in rats have been found after long-term treatment with the Ca^{2+}-blocker nimodipine [20, 38]. Accordingly, physical and mental training through enriched environments, or more direct pharmacological treatment is highly effective in interfering with age-related changes behaviorally and cortically.

Almost certainly, the severe changes in organization and processing of rat sensorimotor cortex must impair tactile perception. Pleger and co-workers could recently demonstrate that in humans the degree of functional organization in somatosensory cortex is linearly related with tactile discrimination abilities [32]. Conceivably, assuming similar drastic changes of cortical organization to occur in elderly human subjects must always certainly lead to severe perceptual impairments. In fact, studies on spatial 2-point discrimination in elderly subjects revealed significant higher discrimination thresholds [43, 48, 49].

To test directly the reversibility, and thus the plastic, adaptive nature of age-related alterations in human subjects, we used a perceptual learning protocol based on coactivation that followed the idea of Hebbian learning: Synchronous neural activity, necessary to drive plastic changes, is evoked by co-activating neighboring skin sites simultaneously [14]. In adults,

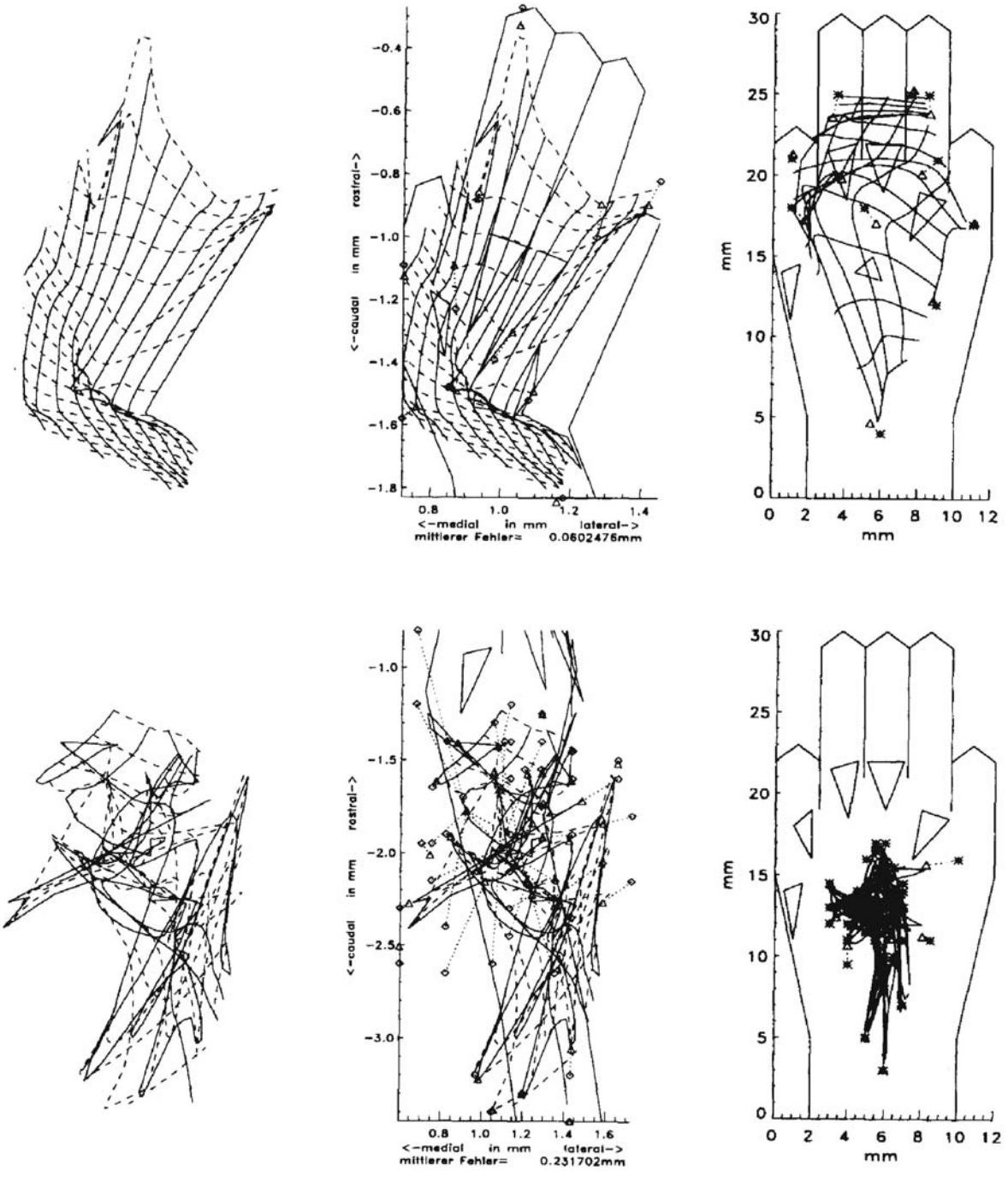

Fig. 2. Effects of age on cortical maps of the hind paw recorded in somatosensory cortex of aged rats. To visualize the effects of aging on the topography of the underlying cortical representations, we reconstructed somatosensory maps using a computer-based interpolation algorithm based on a linear least square approximation of sampling coordinates of penetration sites and corresponding receptive field centers. Reconstruction of a cortical hind paw representation is shown for control (top) and for old rat (bottom), respectively. Examples of cortical topographies represented as a regular lattice within somatosensory cortex (left). Extrapolated cortical representation of a schematic and standardized drawing of the hind paw (middle). Dashed lines indicate horizontal, and solid lines the vertical, components of the lattice. One square of the lattice represents 1 mm^2 skin area. Diamonds indicate penetration sites; squares give the interpolated RF centers. Dotted lines give the deviation between them. Back projection of the regular lattice of the cortical map onto the hind paw (right). Squares give the interpolated, and stars the measured, RF centers. One square of the lattice represents the skin portions that is represented by 0.01 mm^2 cortical area. According to these reconstructions, maps of the hind paw representation recorded in old animals, characterized by a selective impairment of the hindlegs show a dramatic distortion of their representational maps and a loss of topographic order. (Modified from ref. 41; Lippincott Williams & Wilkins)

coactivation of a few hours improves discrimination performance of the coactivated finger [8, 14, 32]. We found similar effects in subjects of high age. In detail, coactivation for 3 hours restored tactile acuity to the level of performance typically seen in subjects 50 years of age [9, 21]. Combined, the results show the general treatability of age-related changes and imply that age-related changes can be reversed even if they have developed.

A comforting outlook

According to the ''Berlin study'', there exists a clear negative correlation between age and measures of intelligence [24]. However, in spite of this overall correlation, the inter-individual variability in the population of subjects that ranged between 70 and 103 years of age, is enormous. As a result, despite the negative correlation, the highest rating in intelligence performance is reached by a woman aged 87. In fact, one of the basic accomplishments in gerontology relate to the acknowledgement of tremendous heterogeneity and inter-individual variability. This variability appears to be a rather general characteristic and has been observed in humans, primates and rats [12, 33]. Additional evidence that aging must not automatically imply a general decline comes from studies of the so-called ''oldest old'', i.e. subjects 100 years and older, who characteristically display a considerable mental and physical fitness. They almost without exception report a high degree of subjective wellness that include active participation in social and cultural life. Interestingly, so far no correlations could be established between events and the individual life-span history on the one hand and the amount of vitality at very high age on the other hand [29].

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The localization of central pattern generators for swallowing in humans – a clinical-anatomical study on patients with unilateral paresis of the vagal nerve, Avellis' syndrome, Wallenberg's syndrome, posterior fossa tumours and cerebellar hemorrhage

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Summary

Background. Our understanding of brainstem swallowing centers is mainly based on experimental animals. In order to solve this problem also in humans, a clinical-anatomical study on dysphagic patients with different lesion patterns was performed.

Patients and methods. We studied 43 consecutively admitted dysphagic patients with unilateral paresis of the vagal nerve (PVN), Avellis' syndrome (AS), Wallenberg's syndrome (WS), posterior fossa tumour (PFT) or cerebellar hemorrhage (CH) with regard to clinical and anatomical aspects.

Findings. There was a continuum with regard to functional outcome from neurogenic dysphagia (ND): Patients with PFT or CH had a significantly worse outcome than patients with WS; the outcome of WS patients was significantly worse than that of patients with PVN or AS. In AS only the Nucleus ambiguus (NA) and its surrounding reticular formation (RF) were affected. In all patients with WS, the infarctions of the dorsolateral medulla were situated in the rostral third of the medulla and affected the NA and the Nucleus tractus solitarii (NTS) with their surrounding RF. In patients with PFT and CH, the NTS and its surrounding RF were affected on both sides. The overlap area of WS and PFT lesions is situated in the NTS and the surrounding RF, especially in its Nucleus parvocellularis.

Interpretation. Our results point to the fact, that in humans the dorsomedial central pattern generators (CPGs) for swallowing are situated in the rostral part of the dorsal medulla oblongata near the NTS/surrounding RF (especially Nucleus parvocellularis) and that the dorsomedial CPGs are superior to the ventrolateral CPGs (near the NA/surrounding RF) with regard to their swallowing-relevance. Furthermore, we hypothesize that – due to the individual asymmetry of the swallowing-dominant forebrain hemisphere – the outcome from ND in WS depends on the side of the medullary infarction.

Keywords: Dysphagia; paresis of the vagal nerve; central pattern generators for swallowing; Avellis' syndrome; Wallenberg's syndrome; posterior fossa tumour; cerebellar hemorrhage.

Introduction

Whereas our knowledge of the cortical representation areas of swallowing in humans has substantially increased during the last few years [4], our understanding of brainstem swallowing centers is mainly based on experimental animals (review: 7). Four central pattern generators (CPGs) for swallowing could be differentiated on both sides of the medulla: two dorsomedial CPGs (DMCPGs) near the Nucleus tractus solitarii (NTS) and two ventrolateral CPGs (VLCPGs) near the Nucleus ambiguus (NA). The DMCPGs contain so-called generator neurons which activate the process of swallowing in timed sequences, whereas switching neurons of the VLCPGs seem to transfer the timed output from the DMCPGs to the cranial nerves V, VII, IX, X and XII, which are involved in swallowing.

On the search for these CPGs in humans, direct methods such as electrical recording, lesioning or mechanical ablations cannot be applied. On the other hand, functional imaging in this brain region is limited with regard to spatial and temporal resolution. One way to solve this problem is to study dysphagic patients with different lesion patterns. For this purpose, we performed MRI examinations in 43 consecutively admitted patients with neurogenic dysphagia (ND) due to unilateral paresis of the vagal nerve (PVN), Avellis' syndrome (AS), Wallenberg's syndrome (WS), posterior fossa (IV. ventricle) tumours (PFT) and cerebellar hemorrhage (CH).

Patients and methods

Recently, we published the results of a prospective study on 208 patients with ND who were admitted to our hospital over a 3-year period for swallowing therapy [10]. In the anatomical part of

this study focussing on the search for human CPGs we performed clinico-anatomical examinations in 43 patients (mean age 62 years, range 24–86 years, SD 12,3; men/women 31/12) with the following etiologies: unilateral PVN (n = 5; carotid endarterectomy: 4, neurinoma of the vagal nerve: 1); AS (n = 3); WS (n = 27); PFT (n = 5; ependymoma grade II: 3, haemangioblastoma grade I: 1, meningioma grade I: 1); CH due to chronic hypertension (n = 3).

Besides clinical, videofluoroscopic (VFSS) and fiberoptic endoscopic examination of swallowing (FEES) an MRI was performed following a standard protocol on a Siemens Magnetom Vision 1.5 Tesla. Transverse, coronal and sagittal T1-, T2-weighted and FLAIR images were carried out on all patients (3 mm thick slices). Depending on the etiology, gadolinium enhancement was additionally performed in T1-weighted images. VFSS and FEES evaluation before and after swallowing therapy was performed following standard protocols including assessment of the degree of penetration/aspiration [10]. For assessing the degree of ND, we used an ordinal scale reflecting the functional feeding status (from 0: full oral without any limitations to 6: totally dependent on tube feeding) as main outcome variable [10]. Wallenberg's syndrome [14] was diagnosed according to criteria published previously [11]. Avellis' syndrome [1] was diagnosed when dysphagic patients suffered from an ipsilateral palato-pharyngo-laryngeal paresis, possibly combined with a contralateral hypalgesia/thermohypaesthesia or hypaesthesia and/or a contralateral hemiparesis in the presence of a typical infarction of the lateral medulla oblongata [12]. The brainstem atlas of Olszewski and Baxter and its nomenclature [8] was used for the identification of brainstem nuclei and pathways. Nonparametric tests were applied (Kruskal-Wallis test, Mann-Whitney U test, Wilcoxon test); statistical significance was set at $p < 0.05$ and corrected according to the Bonferroni procedure.

Results

Upper esophageal sphincter opening, reflex triggering and functional outcome were significantly worse in WS patients as compared to patients with PVN or AS; on the other hand, patients with WS had a significantly better functional outcome than patients with PFT or CH; the latter two groups also showed a severely disturbed reflex triggering and – compared to WS patients – significantly more severely disturbed problems of the oral phase. All patients with PVN or AS became full-oral feeders; 30% of patients with WS remained dependent on tube feeding; five from eight patients with PFT or CH remained dependent on tube feeding and four (two PFT patients with visible medullary lesions and two patients with CH) on a tracheal cannula.

In the three patients with AS (example: Fig. 1 A), the overlap of the infarctions is shown in Fig. 2.

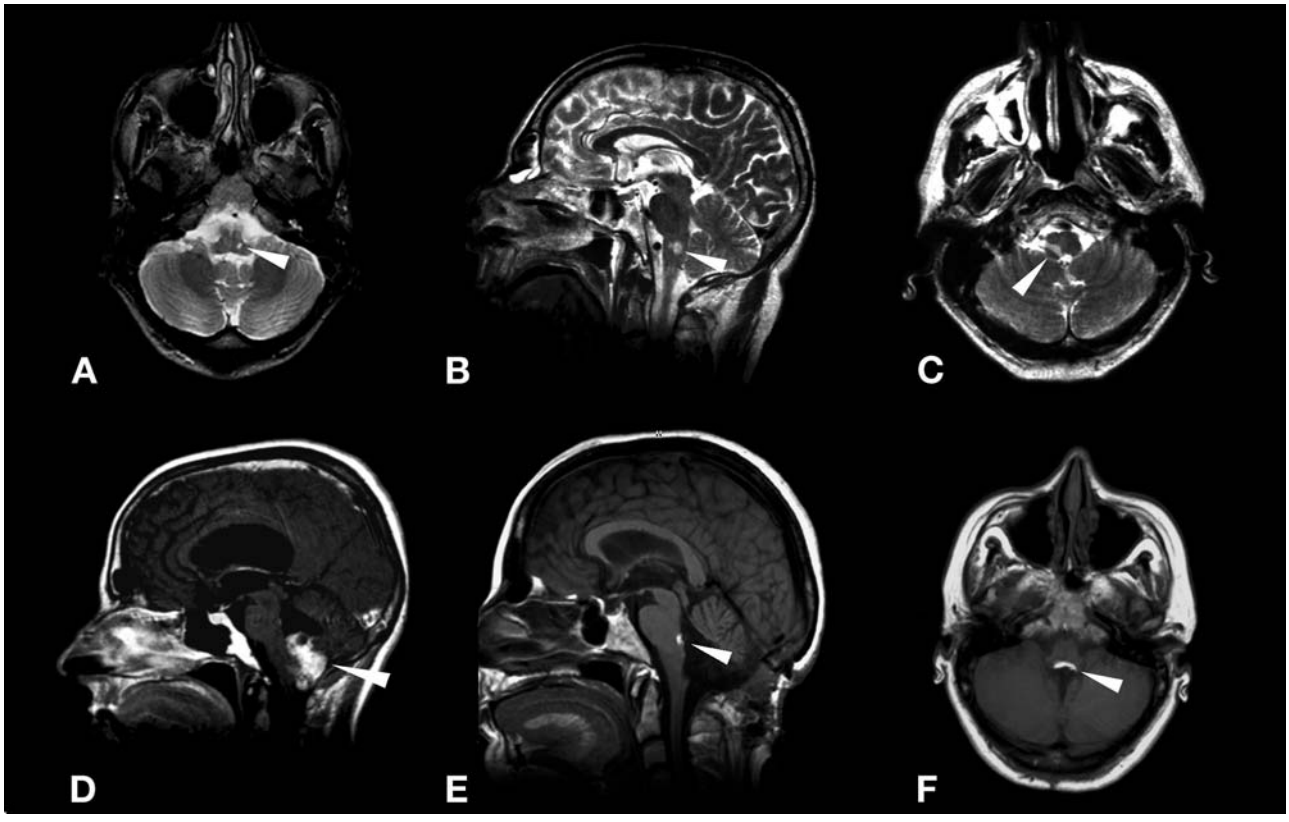

Fig. 1. Top: T2-weighted MRI of a patient with AS (A) and of a patient with WS (B, C). Bottom: T1-weighted MRI of a patient with an ependymoma (grade II, WHO) before (D; with gadolinium) and after removal of the tumour (E, F). Pathological findings are marked by arrowheads (for abbreviations and explanations: see text)

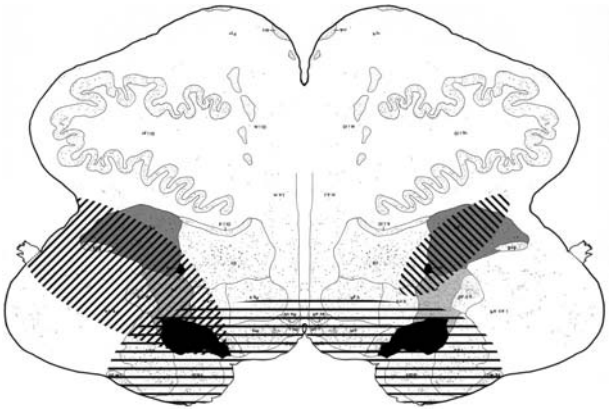

Fig. 2. Rostral medulla oblongata (plate XIV, cross section N° 1801, brainstem atlas of Olszewski and Baxter; 8). Small and black: NA; large and black: NTS; dark gray: Nucleus paragigantocellularis lateralis; light gray: Nucleus parvocellularis; diagonally lined (left): overlap of lesions from patients with WS; diagonally lined (right): overlap of lesions from patients with AS; horizontally lined: overlap of lesions from patients after removal of PFT (for abbreviations and explanations: see text)

Among swallowing-relevant structures only the NA and its surrounding RF is affected. In all patients with WS (example: Fig. 1 B, C), the infarctions of the dorsolateral medulla were situated in the upper third of the medulla; the overlap of the 27 infarctions is also shown in Fig. 2. It can be seen that among swallowing-relevant structures, the NA and the NTS are affected as well as their surrounding RF, especially its Nucleus parvocellularis and paragigantocellularis lateralis.

Two patients with PFT, who developed a severe and longlasting ND, are of special interest. In the first patient (a 65 year old woman), 10 days after removal of an ependymoma (grade II, WHO) a small hemorrhage could be seen in the rostral medulla affecting both sides of the subependymal area including the NTS, the surrounding RF and the XII. nerve nucleus. Therefore, this patient also suffered from a bilateral tongue paresis with atrophy and fibrillations. In the second patient (a 61 year old woman), 7 days after removal of an ependymoma (grade II, WHO) we could also find a small hemorrhage (Fig. 1 D–F). It was located more rostrally than in the first patient and affected the subependymal region of both medullary sides including the NTS, the surrounding RF as well as the Nucleus praepositus, a structure which is not relevant for swallowing. Since the lesion was situated beyond the rostral end of the Nucleus hypoglossus, the patient had no tongue atrophy or any other cranial nerve involvement, but nevertheless suffered from a severe ND.

The overlap area of WS and PFT lesions is situated in the NTS and the surrounding RF, especially in its Nucleus parvocellularis, which might, therefore, be the site of the DMCPGs.

Discussion

There is a continuum with regard to functional outcome from ND in the different groups: All patients with PVN or AS became full-oral feeders; 30% of WS patients remained dependent on tube feeding. Five from eight patients with PFT or CH remained dependent on tube feeding and four persons (two PFT patients with visible medullary lesions and two patients with CH) on a tracheal cannula. Neuroanatomical evaluation showed that in patients with AS the NA and its surrounding RF were involved. This RF region is exactly situated where the VLCPGs are located in animals.

In WS patients, the region of the NA as well as that of the NTS were affected. Since their ND was significantly more severe than in AS, the affection of the NTS/surrounding RF seems to be a more swallowing-relevant anatomical structure than the NA/surrounding RF. Whether the NTS itself or the surrounding RF represents the DMCPG, cannot be surely answered. The rostral and caudal NTS is involved in gustatory and cardiorespiratory functions, respectively. Moreover, the NTS is also an important relais nucleus for visceroafferent and corticobulbar fibers [7], which enables the NTS to modulate swallowing, e.g., dependent on bolus properties. Because of these functions of the NTS, and since the NTS itself is not identical with the DMCPG in animals, it seems more probable that the human DMCPGs are localized within the RF surrounding the NTS (especially the Nuclei parvocellularis and paragigantocellularis lateralis) than in the NTS itself. It has to be emphasized that in all WS patients, the infarction of the dorsolateral medulla was situated in its rostral third. This is in agreement with previous study results showing that ND is much more frequent in WS patients with rostral lesions [5, 13]. We assume that ND is more severe in rostral medullary infarctions because the DMCPGs, i.e. the RF surrounding the NTS, are situated in the rostral medulla and/or because the number of RF cells representing the DMCPGs increases in a caudal to rostral direction (correlating with the increasing extent of the medulla in the same direction). The question arises why despite the same size and location of in-

farctions some WS patients showed a persistent and severe ND, whereas others did not. In this respect, it has to be kept in mind, that more corticobulbar fibers project to the contralateral than to the ipsilateral region of the NTS, as has been shown by Kuypers in humans [6]. Therefore, the side of a medullary infarction may be of relevance: In the case of a left-sided swallowing-dominant hemisphere, more fibers would reach the right medulla with the consequence that, e.g., a left-sided medullary infarction would be correlated with a less severe ND than a right-sided infarction. The contribution of this high number of factors to the development and severity of ND in patients with WS might explain why, according to Sacco *et al.* [11], reports on frequencies of ND in WS vary between 51% and 100% in the literature.

Based on our MRI findings in two patients with visible bilateral lesions of the dorsal medulla (after removal of PFT), it can be assumed, that during the neurosurgical removal of the tumours which were attached at the floor of the IV. ventricle, subependymal (venous?) vessels were hurt. Many veins ramify under the ependyma of the floor of the fourth ventricle; frequently, the median and lateral posterior veins run under the ependyma and are tributaries of the marginal vein of the ventricular floor; more rarely, ramifications of the internal principal anteromedial veins are also found under the ependyma as are those of the lateral group [3]. The overlap of the lesions of these two patients is shown in Fig. 2. It is very probable that affection of DMCPGs was responsible for the severity of the ND in PFT patients. The DMCPGs seem to be situated in the rostral part of the medulla above the rostral end of the XII. cranial nerve nucleus or at least reach into the rostral medullary region (Fig. 1), and/or the number of RF cells representing the DMCPGs increases in a caudal to rostral direction. Recently, a patient with a pure bilateral vascular lesion of the hypoglossal nuclei was described, who showed a good recovery [2]. Therefore, it is improbable that a bilateral lesion of the XII. cranial nerve nuclei alone may be responsible for the severe ND after removal of PFT in one of the patients described above. In one patient with CH, a longlasting ND was described previously [9]; it can be asssumed that in our CH patients posterior-anterior directed pressure caused an (invisible) affection of the DMCPGs with subsequent severe ND, but without any cranial nerve involvement.

The overlap area of WS and PFT lesions is situated in the NTS and the surrounding RF, especially in its Nucleus parvocellularis. This nucleus might be the site of the DMCPGs.

In summary, based on our findings, it can be assumed that in humans the DMCPGs are situated in the RF near the NTS of the rostral medulla (probably in the Nucleus parvocellularis) and are superior to the VLCPGs with regard to their swallowing-relevance. Furthermore, we hypothesize that – due to the individual asymmetry of the swallowing-dominant forebrain hemisphere [4] – the outcome from ND in WS depends on the side of the medullary infarction.

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Functional regeneration of the axotomized auditory nerve with combined neurotrophic and anti-inhibitory strategies

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Summary

Injury to the mammalian auditory nerve is associated with a lack of long-distance elongation and leads to definitive loss of the hearing function. To overcome this central nervous system typical lack of functional regeneration, a combined neurotrophic and anti-inhibitory treatment is applied.

After complete unilateral sectioning of the auditory nerve in adult rats a combination of the Nogo-A inhibitor IN-1 and the neurotrophic factor NT-3 is administrated intrathecally into the cerebello-pontine angle for one week. Functional regeneration is evaluated by measuring auditory brainstem evoked potentials for a follow-up period of up to three months.

After treatment, up to forty percent of the animals showed a second vertex-positive wave in the auditory brainstem evoked potentials which occurred between three to four weeks after sectioning and remained stable during the follow-up period.

A limited degree of functional regeneration of the axotomized auditory nerve is possible after application of IN-1 and NT-3. For additional improvement of functional results further investigations on combined treatments with scar reducing agents, neurotrophic factors and neuroprotective drugs remain necessary.

Keywords: Axonal regeneration; functional regeneration; auditory nerve; cochlear nerve; spiral ganglion; auditory evoked potentials; Nogo-A; NT-3.

Introduction

Injury to the central nervous system (CNS) leads to axotomy of fibre tracts, loss of neurons and glia cells, myelin damage and scar formation [14]. The CNS fibre tracts show a short-lasting sprouting which is accompanied by a growth protein up-regulation of the respective cell bodies. These sprouts present a long-distance regeneration in a peripheral nerve environment [3], but not in CNS tissue [12].

Myelin-associated neurite growth inhibitors have been shown to actively prevent CNS regeneration. Long-distance elongation of descending tracts in the spinal cord of rats could be induced by deleting oligodendrocytes or myelin [13], by intrathecal application of antibodies against the myelin membrane protein Nogo-A [11], or by autoimmunization with myelin [7].

Similar to the situation in the spinal cord, a complete sectioning of the central part of the auditory nerve in the cerebello-pontine angle of adult rats is associated with a lack of long-distance elongation leading to definitive loss of the hearing function [10, 19]. Moreover, a loss of most primary auditory neurons in the spiral ganglion can be observed [17, 18]. Our previous results have shown that inhibition of Nogo-A can induce long-distance elongation of the completely sectioned auditory nerve with regenerated fibres being capable of finding their correct targets in the brainstem [19]. We have also demonstrated already that the intrathecal application of a neurotrophic factor (NT-3) can significantly increase the number of surviving auditory neurons in the spiral ganglion [18].

In the present study, the previously applied anti-inhibitory (Nogo-A) and neurotrophic (NT-3) strategies are combined to examine the effects on functional regeneration after complete sectioning of the mammalian auditory nerve.

Material and methods

Ten adult Lewis rats (aged eight weeks) were anaesthetised by intraperitoneal injection of ketamine (80 mg/kg) and xylazine (14 mg/kg) and underwent sharp transection of the left auditory nerve via a microsurgical suboccipital approach.

Five rats were treated with a cocktail of the Nogo-A inhibitor (Fab fragment of the IN-1 antibody) and the neurotrophic factor NT-3. Intrathecal application was delivered via osmotic minipumps at a constant rate of 1 µl/h for one week (Alzet Model 2001, Alza

Corp., Palo Alto, California). Further application details have been specified previously [18, 19]. Five rats served as untreated controls. Approval of the experimental protocol concerning the use and care of the laboratory animals was obtained from the institutional animal care and use committee.

Auditory brainstem response (ABR) recording was performed immediately after and 30 minutes following auditory nerve section. Follow-up examinations were performed for up to three months. Click stimuli of 90 db intensity were generated in alternate polarity, condensation and rarefaction mode driven by rectangular pulses of 100 μs duration (model ACB-1; Walter, Germany). The stimuli were presented monaurally (Nicolet TIP-10 tubal earphones). Stimulus repetition rate was 13.2 pulses per second. The non-stimulated ear was masked by 70 db white noise. The ABR was recorded using 4 subcutaneous needle electrodes, electrophysiological responses were amplified (×20.000) with filters set at 10 to 5000 Hz. 1024 sweeps of 10 ms duration with pre-stimulus period of 2 ms were averaged per run. Further details have been specified previously [10].

Results

ABR waveforms to left and right-sided stimulation did not significantly differ before auditory nerve sectioning between the studied animals. After nerve sectioning, waveforms of the undamaged right side remained unchanged to stimulation, while wave Ib to wave IV of the ABR disappeared on the sectioned left side in all animals. In one animal of the control group even wave Ia disappeared on the sectioned side. In two of the treated rats a second vertex-positive wave occurred within three to four weeks after trauma. This second vertex-positive wave had a mean latency of 2.7 ms (SD: 0.14 ms, $p < 0.001$) and remained stable throughout the follow-up period. During this time no further waves occurred.

Discussion

Injury to the mammalian auditory nerve is associated with a lack of functional regeneration and leads to definitive loss of the hearing function [10, 17] associated by a loss of most primary auditory neurons in the spiral ganglion [17, 18]. Previous studies have shown that inhibition of Nogo-A can induce long-distance regeneration of the axotomized auditory nerve with elongating fibres being capable of finding their correct targets in the brainstem [19]. In addition, a significant increase of the number of surviving auditory neurons in the spiral ganglion has been achieved after the intrathecal application of a neurotrophic factor (NT-3) [18].

Consequently, the present study has analysed the impact of a combined application of IN-1 and NT-3 strategies on functional regeneration after complete sectioning of the mammalian auditory nerve. The observed occurrence of a second vertex-positive ABR wave in two of five treated animals three to four weeks after sectioning indicates an activation of second-order neurons in the brainstem by regenerating auditory nerves. These signs of functional regeneration are still limited as no further waves could be generated during the follow-up period of up to three months. These results are in line with our morphological observation reported previously [18, 19].

Presently, even more promising results are reported in the field of spinal cord regeneration following the same treatment strategy. After antibody-mediated neutralization of Nogo-A [1, 2, 11], Nogo gene deletions [5, 8, 16], NgR receptor blockade [6, 9, 21] or blockade of the downstream messengers Rho-A and ROCK [4, 5], impressive enhancement of long-distance regeneration and functional recovery have been reported in the rat and mouse model (reviewed in 15). Similar to the present study, a combined application of IN-1 and NT-3 was performed successfully to promote chronically injured corticospinal tracts [20].

Therefore, Nogo-A obviously plays a major role in the limited spontaneous regeneration capabilities in the CNS. However, the relations of different inhibitory components in the CNS, their precise interaction modes and the optimal ways to influence them have still to be explored before a clinical application of these experimental results is possible.

Conclusion

A limited degree of functional regeneration of the axotomized auditory nerve is possible after antibody-mediated neutralization of Nogo-A and application of NT-3. For additional improvement of functional results further investigations on combined treatments with scar reducing agents, neurotrophic factors and neuroprotective drugs remain necessary.

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Electrically evoked hearing perception by functional neurostimulation of the central auditory system

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Summary

Perceptional benefits and potential risks of electrical stimulation of the central auditory system are constantly changing due to ongoing developments and technical modifications. Therefore, we would like to introduce current treatment protocols and strategies that might have an impact on functional results of auditory brainstem implants (ABI) in profoundly deaf patients.

Patients with bilateral tumours as a result of neurofibromatosis type 2 with complete dysfunction of the eighth cranial nerves are the most frequent candidates for auditory brainstem implants. Worldwide, about 300 patients have already received an ABI through a translabyrinthine or suboccipital approach supported by multimodality electrophysiological monitoring. Patient selection is based on disease course, clinical signs, audiological, radiological and psycho-social criteria.

The ABI provides the patients with access to auditory information such as environmental sound awareness together with distinct hearing cues in speech. In addition, this device markedly improves speech reception in combination with lip-reading. Nonetheless, there is only limited open-set speech understanding.

Results of hearing function are correlated with electrode design, number of activated electrodes, speech processing strategies, duration of pre-existing deafness and extent of brainstem deformation.

Functional neurostimulation of the central auditory system by a brainstem implant is a safe and beneficial procedure, which may considerably improve the quality of life in patients suffering from deafness due to bilateral retrocochlear lesions.

The auditory outcome may be improved by a new generation of microelectrodes capable of penetrating the surface of the brainstem to access more directly the auditory neurons.

Keywords: Hearing aid; neuroprosthesis; functional neurostimulation; auditory brainstem implant; electrical stimulation; cochlear nucleus.

Introduction

Electrical neurostimulation of the central auditory system in patients with bilateral retrocochlear deafness was first applied in 1979 by William House and colleagues [3, 6]. Since this pioneering work, almost 300 profoundly deaf patients have received an auditory brainstem implant (ABI) for partial restoration of hearing function.

Most of the patients treated with an ABI have bilateral vestibular schwannomas which cause complete dysfunctional eighth cranial nerves. Although there have been major improvements in the prevention of bilateral deafness by function-conserving microsurgery of schwannomas and radiosurgery, there is no alternative treatment option when the auditory nerve has lost its function either by surgery or by tumor growth. Bilateral vestibular schwannomas typically occur in patients suffering from neurofibromatosis type 2. Other potential candidates for ABI are patients with lateral skull base fractures leading to bilateral cochlear nerve injuries or patients with deafness due to congenital cochlear disease, bilateral congenital aplasia of the cochlear nerve or bilateral cochlear ossification.

In all these patients standard hearing aids and prostheses (like cochlear implants) are not effective. The ABI bypasses both the cochlea and the eighth nerve and directly stimulates neurons of the central auditory pathway. Potentially, several sites at the brainstem are available for functional neurostimulation. Traditionally, the second-order neurons of the cochlear nucleus are the main targets of ABIs, generally because they are relatively simple to access after surgical removal of vestibular schwannomas.

Current technique and strategy

In auditory brainstem implants a microphone located near the ear retrieves the sounds and transmits

them to a speech processor, which digitizes them into coded signals. This processor is connected to a transmitting coil, which sends the signals to a subcutaneous implant. From here electrical signals are forwarded to an electrode array which is designed to be placed into the lateral recess of the fourth ventricle and to stimulate the cochlear nucleus.

The general design and function of ABIs is comparable to that of cochlear implants. The main differences focus on the shape of the stimulating electrode array. The speech processor needs to be adjusted to the individual patient in both hearing aids. Especially in ABIs, this programming process may take weeks and even months in order to achieve optimal parameters of electrically induced auditory percepts. In cochlea implants the neural stimulation can be standardised due to the homogeneous tuning of neurons in the cochlea. In contrast, ABIs have to adapt to the interindividual variability of the brainstem anatomy, particularly in patients with vestibular schwannomas. This has let to the evolution of multichannel auditory implants to accommodate variations in the anatomy of the lateral recess in these patients.

While the first ABI worked by a bipolar electrode connected to a single channel implant, recent multichannel implants can utilize more than 20 electrodes allowing for more individualized stimulus patterns to code frequency cues. As some of these electrodes lead to side effects during stimulation, only a selected number of them are in continuous use. This evolution in electrode design has been accompanied by a significant improvement in perceptional performance.

The surgical technique for ABI implantation includes either the translabyrinthine or the suboccipital approach. While the translabyrinthine approach offers a better angle onto the lateral recess, the suboccipital route provides a broader access to large vestibular schwannomas and to a distorted brainstem anatomy. Independent of the approach, successful ABI implantation can be performed on the basis of a refined surgical technique.

Multimodal electrophysiological monitoring should be performed for correct electrode placement, especially in distorted brainstem anatomy. Thereby, adverse side effects and stimulation of other cranial nerves can be minimized. By selectively activating different electrodes on the array, the extension of the cochlear nucleus can be mapped to optimize the best possible electrode position for stimulation.

Current functional results

ABIs help to differentiate between rhythm, stress and simple words. Using this device, it is even possible to discriminate between temporal and spectral patterns in speech to some degree. This allows distinguishing various voice qualities especially in quiet surroundings [2, 10, 14–16]. Recent speech encoders facilitate high-rate coding strategies with the potential of a better representation of temporal information [7, 10, 14, 15].

Nonetheless, in an open-set condition the patient's performance declines when relying barely on auditory information although speech can be discriminated from environmental sounds in most of the cases. In combination with visual information, the ABI supplies an overall enhancement of lip-reading capabilities [7, 12].

Non-auditory responses like mild tingling or stitch sensations in the face or body are observed temporarily during initial stimulation. By changing the stimulation mode and reprogramming the device these side effects can be eradicated [14, 15].

However, even in multichannel ABI devices the quality of sound does not reach the levels achieved with similar cochlear implants [2, 10, 14–16].

Often, patients with different performance levels in auditory tests report similar degrees of satisfaction with the implanted device. Realistic expectations increase patients' judgment of the helpfulness of ABI. Therefore, extensive counselling of ABI candidates is mandatory before implantation [9].

Discussion

A variety of individual factors influence the perceptional performance of patients with ABIs. Long duration of deafness with a decreased number of functional neurons in the cochlear nucleus as well as anatomical variations due to pre-existing brainstem deformation is predictive of a less favourable outcome. Patients' expectations and their ability to make the most of modest auditory cues define their satisfaction with the implanted auditory device [7, 12].

Decisive for the outcome is the correct identification of the implant site [1, 8, 12], which should be supported by multimodality monitoring for precise implant positioning and exclusion of side effects [5, 15, 17]. However, the hearing performance and the quality of sound in ABIs are still not comparable to the level obtained with cochlear implants despite new speech process-

ing strategies and an increased number of stimulating electrodes [10, 14, 15]. This is mainly caused by the three-dimensional tonotopic order of the cochlear nucleus, which makes proper functional neurostimulation with surface electrodes difficult and diminishes the hearing performance in ABI patients [7, 14, 15].

These shortcomings have led to the development of a new generation of auditory prostheses with microelectrodes capable of penetrating the cochlear nucleus safely with very limited damage. Experimental studies in animals have shown that penetrating electrodes are able to access more directly the tonotopic order of the cochlear nucleus leading to an increased range of spectral cues and to a reduced threshold for electrical stimulation of the auditory system [4, 11, 13]. Whether improved biophysical parameters result in benefits for ABI patients has to be examined in clinical trials to come.

Conclusion

Electrical neurostimulation of the cochlear nucleus with multichannel surface ABI is sufficient for providing a functionally beneficial level of auditory information. ABI supports profoundly deaf patients with environmental awareness and enhances their lip-reading capabilities especially in communication with familiar speakers.

Refined stimulation patterns, modified speech processing strategies and improved three-dimensional electrode array designs will hopefully contribute to an evolution of auditory perception in patients with central auditory prosthesis.

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Physiological recordings from electrodes implanted in the basal ganglia for deep brain stimulation in Parkinson's disease. The relevance of fast subthalamic rhythms

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Summary

Deep brain stimulation electrodes implanted in the subthalamic nucleus of patients with Parkinson's disease allow electrophysiological recordings from the human basal ganglia. Subthalamic local field potential recordings revealed the presence of multiple rhythms, from the classical EEG frequency range (<50 Hz), to surprisingly high frequencies (70 Hz and 300 Hz). Fast rhythms are particularly attractive because of their likely interaction with the excitatory mechanisms of action of deep brain stimulation. Here we investigated whether the two rhythms at 70 Hz and at 300 Hz represent distinct modes of operation, and therefore different targets, within the subthalamic nucleus. We retrospectively analyzed the dataset we used to describe the 300 Hz rhythm (Foffani, Priori *et al.*, Brain 126: 2153–2163, 2003) searching for significant 70 Hz oscillations after levodopa administration. Whereas (as previously reported) 300 Hz activity was a consistent feature in the dataset, significant 70 Hz activity was observed in only 2 of 11 nuclei. Therefore, 70 Hz oscillations are not a necessary condition for the presence of 300 Hz oscillations. The two rhythms probably arise from different mechanisms, reflecting different functional and/or spatial aspects of subthalamic pathophysiology. Fast subthalamic oscillations could be exploited for intra-operative electrophysiological monitoring of the subthalamic nucleus, post-operative confirmation of electrode placement and patient-specific 'reglage' of the electrical parameters for chronic deep brain stimulation.

Keywords: STN; DBS; local field potentials; L-DOPA; basal ganglia; Parkinson's disease; human.

Introduction

The advent of deep brain stimulation of the subthalamic nucleus for treating Parkinson's disease opened a unique window of opportunity to record local field potentials (i.e. deep EEG activity) from the basal ganglia in living humans. The analysis of local field potentials recorded from the subthalamic nucleus of parkinsonian patients revealed the presence of multiple rhythms, ranging from the classical EEG frequency range (<50 Hz) [1, 5, 7, 9] to surprisingly high frequencies, around 70 Hz [1, 2] and around 300 Hz [3]. Subthalamic rhythms are differentially modulated by movement [2–5, 7] and dopamine [1, 3, 5, 9], which supports their pathophysiological significance. The precise localization of these rhythms within the subthalamic nucleus [1, 3, 5] suggests that they could have specific electrophysiological significance for functional neurosurgery. Fast rhythms are particularly attractive from a clinical point of view because of their possible involvement [1, 3] in the excitatory mechanisms of action of deep brain stimulation. Here we investigated whether the two rhythms at 70 Hz and at 300 Hz represent distinct modes of operation, and therefore different targets, within the subthalamic nucleus. With this purpose, we retrospectively analyzed the dataset we used to describe the 300 Hz rhythm [3] searching for significant 70 Hz oscillations, in order to compare the relative consistency of the two rhythms.

Materials and methods

Experimental protocol

The patients, the methods for the localization of deep brain stimulation electrodes (model 3389 Medtronic, Minneapolis, USA)

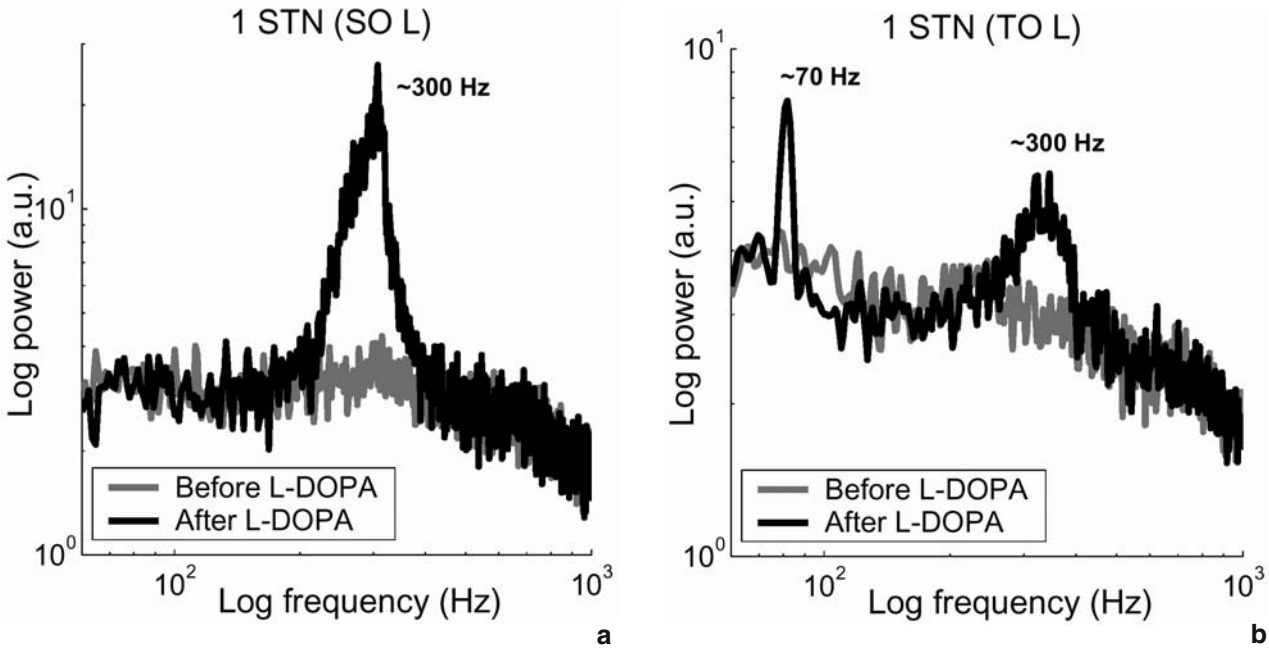

Fig. 1. Fast oscillations in the human subthalamic nucleus. Examples of (a) 300 Hz oscillations and (b) coexistence of 70 Hz and 300 Hz oscillations in the 'on' state after levodopa administration. The figures represents the high-frequency (60–1000 Hz) spectrum in two subthalamic nuclei from two patients before (gray line) and after (black line) levodopa (L-DOPA) administration. 70 Hz oscillations were observed only in 2 of 11 nuclei, whereas 300 Hz oscillations were a consistent phenomenon after dopaminergic medication [5]

within the subthalamic nucleus, and the post-operative recording procedures are fully described in our previous work [3]. Briefly, electrode localization procedures included (a) the pre-operative direct visualization of the nucleus through CT-MRI targeting, (b) the intra-operative neurophysiology with microrecordings [8], intra-operative stimulation (i.e. through the explorative microelectrode) and macrostimulation (i.e. through the implanted macroelectrode), (c) the post-operative CT-MRI verification of the final electrode position, and (d) the post-operative clinical assessment of the optimal DBS contact. The postoperative recording sessions took place 2–3 days after the electrode implantation, after overnight withdrawal of antiparkinsonian medication. Here we considered only local field potentials recorded while the patients were at rest, before and after administration of levodopa [Table 1 in [3]; 11 nuclei from 7 patients].

Data analysis

The 70 Hz oscillatory activity of the subthalamic nucleus was quantified by power spectral analysis of the recorded local fields potentials, extending the analyses we performed in our previous work [3]. The spectra were calculated using the Welch's averaged modified periodogram method (Matlab function ''psd''), after normalizing the signals to their high-frequency (600–1000 Hz) content. The following test was performed for each nucleus: (i) the relative spectrum (after medication/before medication) was calculated; (ii) a threshold was set at the mean plus three standard deviations of the 600–1000 Hz relative spectrum; (iii) 70 Hz activity was considered significant if the peak of the relative spectrum between 60 Hz and 90 Hz exceeded the threshold. Note that in all 11 nuclei considered, we previously reported significant 300 Hz activity [3].

Results

We retrospectively analyzed local field potentials recorded from 11 subthalamic nuclei in 7 parkinsonian patients before and after levodopa administration from a dataset previously published, in which 300 Hz activity was always present after levodopa [3]. Significant 70 Hz activity was observed only in two nuclei after levodopa administration (<20%). Figure 1a shows a typical example of 300 Hz oscillations without 70 Hz oscillations (from a nucleus not present in the original dataset). Figure 1b shows an example of coexistence of 70 Hz and 300 Hz oscillations in the human subthtalamic nucleus. It was not possible to correlate 70 Hz oscillations with any evident clinical specificity.

Discussion

Subthalamic rhythms in the classical EEG frequency range (<50 Hz) have been described before and after dopaminergic medication by different groups [1, 5, 7, 9]. Conversely, 70 Hz subthalamic oscillations

have been reported so far only by Brown and colleagues [1, 2] and 300 Hz oscillations only by our group [3]. The physiological significance of these fast oscillations has been related to ''attentional processes operating in the executive domain'' [1], and to a non-specific regulation of neural synchrony for high-resolution information processing within the basal ganglia circuit [3]. Here we show that 300 Hz oscillations do not depend on the presence of 70 Hz oscillations. Indeed, 70 Hz and 300 Hz oscillations can coexist and the two rhythms probably arise from different mechanisms.

Two main and not mutually exclusive reasons could account for the different consistency of 70 Hz and 300 Hz subthalamic oscillations. The first possibility is that these two rhythms represent different *functional* aspects of the pathophysiology of the subthalamic nucleus in Parkinson's disease. Accordingly, differences in the clinical or experimental state of the patients (such as the inclusion criteria, the time of recording after surgery or the specific response to dopaminergic medication during the experiments) could generate different patterns of fast subthalamic oscillations. The second possibility is that 70 Hz and 300 Hz oscillations represent different *spatial* aspects of subthalamic activity. Following this interpretation, the subthalamic nucleus should not be considered as a single homogeneous structure, but more as a complex nuclear aggregate with multiple subsystems operating at different frequencies [9].

Although the cellular mechanisms of fast subthalamic oscillations are unclear [3], these rhythms have potential significance for functional neurosurgery. First, oscillatory activity detected by spectral analysis can be used as a simple approach for electrophysiologically monitoring the subthalamic nucleus during surgery for Parkinson's disease [6]. In addition, the consistency of 300 Hz oscillations and their precise localization within the subthalamic nucleus [3] could be exploited as a post-operative electrophysiological confirmation of electrode placement, complementary to more sophisticated imaging techniques. Finally, if 70 Hz and 300 Hz oscillations are harmonically excited by deep brain stimulation and directly contribute to the clinical efficacy of the therapy [1, 3], their central frequency, height and bandwidth [3] could serve as objective measures for a patient-specific 'reglage' of the stimulation parameters. In conclusion, physiological recordings from electrodes implanted in the human basal ganglia could have not only a pathophysiological significance, but also a direct relevance for the neurosurgical and clinical aspects of deep brain stimulation.

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DBS therapy for the vegetative state and minimally conscious state

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Summary

Twenty-one cases of a vegetative state (VS) and 5 cases of a minimally conscious state (MCS) caused by various kinds of brain damage were evaluated neurologically and electrophysiologically at 3 months after brain injury. These cases were treated by deep brain stimulation (DBS) therapy, and followed up for over 10 years. The mesencephalic reticular formation was selected as a target in 2 cases of VS, and the CM-pf complex was selected as a target in the other 19 cases of VS and 5 cases of MCS. Eight of the 21 patients emerged from the VS, and became able to obey verbal commands. However, they remained in a bedridden state except for 1 case. Four of the 5 MCS patients emerged from the bedridden state, and were able to enjoy their life in their own home. DBS therapy may be useful for allowing patients to emerge from the VS, if the candidates are selected according to appropriate neurophysiological criteria. Also, a special neurorehabilitation system may be necessary for emergence from the bedridden state in the treatment of VS patients. Further, DBS therapy is useful in MCS patients to achieve consistent discernible behavioral evidence of consciousness, and emergence from the bedridden state.

Keywords: vegetative state; minimally conscious state; deep brain stimulation; CM-pf complex; evoked potential; EEG.

Introduction

The Multi-Society Task Force on PVS (1994) [6, 7] summarized the medical aspects of the vegetative state (VS) [3]. They provided the statement that the VS is a clinical condition of complete unawareness of the self and the environment, accompanied by sleep-wake cycles, with either complete or partial preservation of hypothalamic and brainstem autonomic function. In addition, patients in a VS show no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; show no evidence of language comprehension or expression; have bowel and bladder incontinence; and have variably preserved cranial-nerve and spinal reflexes. On the other hand, the definition and diagnostic criteria of the minimally conscious state (MCS) were reported in 2002 [2]. The MCS is characterized by inconsistent but clearly discernible behavioral evidence of consciousness and can be distinguished from coma and the VS by documenting the presence of specific behavioral features that are not found in either of these latter conditions.

We have applied deep brain stimulation (DBS) therapy for the treatment of patients with prolonged loss of consciousness extending over 3 months, and 26 cases were followed up for over 10 years [5, 8–11]. Retrospectively, these cases were classified into VS (21 cases) and MCS (5 cases) according to the above statements on the PVS and MCS. They remained in a VS or MCS for more than 3 months after sustaining various kinds of brain damage. Between the VS and MCS patients, the long-term effects of DBS therapy were assessed comparatively.

Materials and methods

The present 26 cases which included VS (21 cases) and MCS (5 cases) were evaluated neurologically and electrophysiologically at 3 months after brain injury and were treated by DBS therapy. We followed these cases up for over 10 years, and examined their long-term functional recovery. The ages of the VS patients ranged from 19 to 75 (mean = 44.0) years old, and the causes of the initial coma were head injury (9 cases), cerebrovascular accident (9 cases) and anoxia (3 cases). The ages of the MCS patients ranged from 18 to 47 (mean = 33.5) years old, and the causes of the initial coma were head injury (3 cases) and cerebrovascular accident (2 cases). At 3 months after the onset of the comatose state, neurological examinations and neurophysiological evaluations were carried out. The neurophysiological evaluations included assessments of the auditory brainstem response (ABR), somatosensory evoked potential (SEP), pain-related P250 and continuous EEG frequency analysis [5, 8–11].

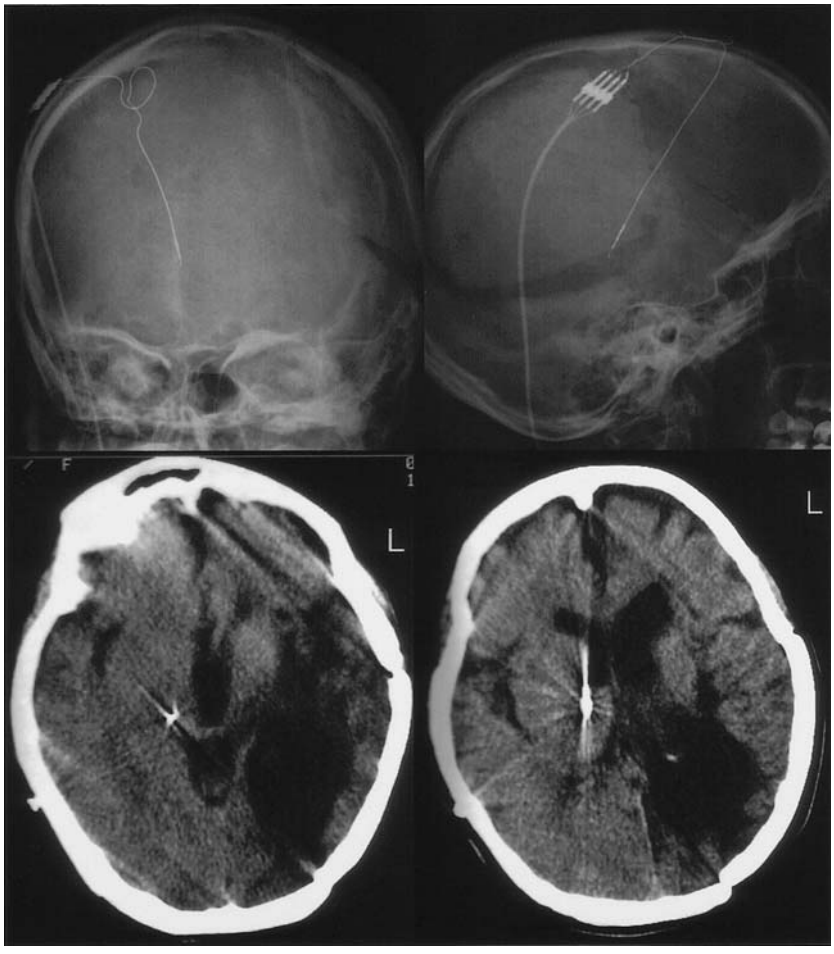

Fig. 1. Computerized tomography and x-ray films showing the deep brain stimulation electrode for the treatment of a vegetative state patient. The stimulating electrode was implanted for CM-pf stimulation

Chronic DBS was applied using a chronically implanted flexible wire electrode inserted by stereotaxic surgery under local anesthesia. As target points for the VS, the mesencephalic reticular formation (2 cases) and the CM-pf complex (19 cases) were selected, while the CM-pf complex (5 cases) was selected for the MCS. Stimulation was given every 2 to 3 hours during the daytime, and was continued for 30 min at one time. The frequency of the stimulation was mostly fixed at 25 Hz, and the intensity was decided according to the responses of each individual patient, being at slightly higher than the threshold for inducing an arousal response. To apply the chronic DBS, we employed a chronically implanted flexible electrode (3380, Medtronic Co.) and a transmitter-receiver system (3470 and 3425, Medtronic Co.). The target point in the mesencephalic reticular formation was the nucleus cuneiformis, which is located in the dorsal part of the nucleus ruber and ventral part of the deep layer of the superior colliculus. The CM-pf complex was selected as the stimulating point in the non-specific thalamic nucleus (Fig. 1).

Results

Effects of DBS for the VS

Eight of the 21 cases emerged from the VS, and could communicate with some speech or other responses, but needed some assistance with their everyday life in bed. Even after long-term rehabilitation, their state of being bedridden remained unchanged in 7 of these 8 cases. The other 1 case became able to live in a wheel-chair (Fig. 2). The other 13 cases were unable to communicate at all and failed to emerge from the PVS. In the 8 cases that emerged from the PVS following DBS therapy, the Vth wave of the ABR and N20 of the SEP were recorded even with a prolonged latency; continuous EEG frequency analysis demonstrated a desynchronization pattern or slight desynchronization pattern; and the pain-related P250 was recorded with an amplitude of over 7 μV.

Effect of DBS for the MCS

All of the 5 cases of MCS were able to display inconsistent behavioral evidence of consciousness before DBS therapy, and they became able to communicate with definite behavioral responses after the DBS. Four cases emerged from the bedridden state, and were able

Fig. 2. Patient who emerged from the vegetative state, riding in a wheel-chair, and writing numbers on a paper (a). The numbers were correctly written on the paper (b)

to enjoy their life in their own home. The other 1 case still remained in a bedridden state. Electrophysiological evaluations of these 5 cases revealed the following: the Vth wave of the ABR and N20 of the SEP were recorded even with a prolonged latency; continuous EEG frequency analysis demonstrated a desynchronization pattern; and the pain-related P250 was recorded with an amplitude of over 7 μV.

Discussion

DBS applied to the mesencephalic reticular formation or CM-pf complex can exert a strong arousal response and elicit marked increases in r-CBF and r-CMRO2 [8, 9]. In the PVS, cerebrocortical functions are more disturbed than brainstem functions, and the relationship between the brainstem and cerebral cortex is important for maintaining consciousness. On this basis, we mainly selected the CM-pf complex for DBS therapy, in view of the fact that electrical stimulation of the CM-pf complex is known to induce incremental recruiting and an augmenting response of the EEG with low-frequency stimulation, and EEG desynchronization with high-frequency stimulation [1, 4].

The DBS therapy for the VS was not sufficiently effective to allow all cases to emerge from the VS. We stress that chronic DBS therapy may be useful for enabling patients to emerge from a VS, if the candidates are selected according to appropriate neurophysiological criteria. The 8 cases that did emerge from the VS were all in a bedridden state for a long-term period, and only 1 patient recovered sufficiently to live in a wheel-chair. In addition to the DBS therapy, we consider that a special neurorehabilitation program may be necessary for the treatment of patients in a VS.

We have usually applied chronic spinal cord stimulation (SCS) for treatment of the MCS and not for the VS. Indeed, we have applied DBS for treatment of the MCS in only 5 cases. In comparison with the VS patients, the MCS patients showed remarkable functional recovery, emerged from the bedridden state, became able to speak correctly, and to enjoy their life in their own home. Clinical application of DBS therapy for the MCS is expected to accelerate recovery from this state. In our experience, SCS is also effective for MCS patients. However, there are several points of difference between DBS of the CM-pf complex and SCS. Stimulation of the CM-pf complex can induce a strong arousal response immediately after the start of stimulation: however, SCS cannot induce such a strong arousal response. In neural activation studies employing near infrared spectroscopy (NIRS), stimulation of the CM-pf complex has been shown to elicit marked and long-lasting increases in total-Hb and Oxy-Hb as compared to SCS.

We have classified patients into the VS or MCS at the time of 3 months after the onset of brain injury, since most of the spontaneous recovery occurs within the first 3 months. When we assess the effects of each of the treatments, the most important factor is the time period from the onset of brain injury. The VS diagnosed at 1 month, 3 months, or 6 months after the onset of brain injury constitutes quite different states, and quite different long-term follow-up results tend to be observed. We should therefore stress the time period after the onset of brain injury, when we discuss the

long-term follow-up results. We can employ DBS and SCS for treatment of the VS and SCS, and the indications should be considered in the light of neurological and electrophysiological examinations. Not only the classification of the neurological state such as into the VS or MCS, but also the time period after the onset of brain injury should be taken into account in the treatment of such patients.

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Deep brain stimulation for idiopathic or secondary movement disorders

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Summary

Deep brain stimulation has gained increasing interest in the treatment of movement disorders. Presenting our clinical series of 179 patients operated upon since 1999, the indications, risks and benefits for the patients are discussed in order to further imporve the techniques and their applications.

Keywords: Deep brain stimulation; Parkinson's disease; movement disorders.

Introduction

Neurosurgical therapy for movement disorders has recently gained once more increasing interest due to the shift from destructive procedures to stimulation related treatment options. Benabid *et al.* [1] reported in 1993 the first series of 87 patients among whom were 61 with Parkinson's disease (PD), 13 with essential tremor (ET) and, 13 with hyperkinetic syndromes of various origins who had been treated with deep brain stimulation of the ventral intermediate nucleus of the thalamus (VIM). A better neurosurgical experience with this technique and more recent models of basal ganglia function, that underline the origin of the cardinal features of Parkinson's disease establishing that hyper activity of the subthalamic nucleus (STN) is an essential feature of the Parkinsonean state [11], have shifted the interest in DBS from VIM to the GPI and also to STN. While PD is mainly considered an idiopathic disorder, a secondary – sometimes traumatic – origin, based on clinical experience, has also been postulated for this and other movement disorders. In this short review, our experience gained over the last 5 years will be summarized with special emphasis on surgical aspects.

Clinical series

In the Department of Neurosurgery at the University of Kiel Medical Center a Deep Brain Stimulation (DBS) program was initiated in 1999 in close cooperation with the Department of Neurology in order to expand therapeutical options for movement disorder patients. During the period from january 1999 until august 2004, 179 patients were operated upon in accordance with the DBS program. The indications for surgery as well as contraindications are summarized in Tables 1a,b. The various steps of the surgical pro-

Table 1. *a. Indications for deep brain stimulation in Parksinons' disease*

Levodopa induced motor fluctuations	Levodopa induced dyskinesias
Wearing off:	*Off-period-dystonias:*
end-of dose, noctural or early morning akinesia	early morning or dyskinesia in the daytime
On-off-fluctuations:	*On-period-dykinesias:*
sudden predictable or unpredictable, yo-yoing	peak-dose-dyskinesia, biphasic dyskinesias
Short duration, increased latency or no response	(beginning and/or end-of-dose dyskinesias)
Freezing	*Other dyskinesias (rare):*
Rebound superparkinsonism	e.g. myoclonus, tics

Table 1. *b. Indications and contraindications*

Inclusion criteria
idiopathic PD, conservatively treated, positive L-Dopa test
good general health
Exclusion criteria
severe brain atrophy, multiple hyperintense signals on T2-weighted MRI
severe cerebral macroangiopathy
no pseudobulbar side effects (e.g. post previous PD surgery)
dementia (MMS $\leq$ 24/30, Mattis scale $\leq$ 130)
severe frontal lobe dysfunction, poor cooperation
severe, uncontrollable internal disease
anticoagulant therapy, immunosuppression

Table 2. *Surgical procedure*

Patient selection – L-Dopa test
MRI – direct visualization of STN and trajectory
CT – to exclude/compensate for MR distorsion
Target selection acc. to MRI and electrophysiology
5 parallel trajectories (Ben's gun modified)
Microelectrodes recording "downwards"
Microelectrodes stimulation "upwards"
Macroelectrode implantation & test stimulation
Stereotactic X-ray postop
MRI control
A few days later setting the IPG

cedure are listed in Table 2. The majority of patients suffered from levodopa responive PD complicated by motor fluctuations and/or dyskinesias. These patients underwent a standardized presurgical neurological evaluation. Secondary movement disorders were diagnosed in 5 out of 35 patients with dystonia or tremor who were subjected to deep brain stimulation. In two patients a clear history of trauma was present, in two patients a generalized hypoxia had occurred either perinatally or during tonsillectomy, in the latter patient age at 22 producing a Lance Adam's syndrome. In the fifth patient intoxication was the cause of dystonia.

Technique of deep brain stimulation

Deep brain stimulation is performed using established stereotactic frame based techniques together with intraoperative microelectrode recording and stimulation through both the temporary microelectrodes and the permanent macroelectrode. Initially, much debate was raised on the correct target imaging. Since conventional basal ganglia anatomy as described by Schaltenbrand, Wahren [12] and others [15, 18] was always referenced to the AC-PC line as defined by ventriculography, this technique had to be considered the gold standard. This, however, required also intraoperative stereotactic X-ray not available in most operating rooms. Furthermore, with the advent of modern computing hard- and software facilities and modern imaging techniques such as computed tomography and, mostly, magnetic resonance imaging (CT resp. MRI), it became possible to apply these imaging techniques to functional neurosurgery [3]. This, on the one hand, necessitated the correlation between CT and MRI coordinates to compensate for a possible distorsion of the MR image obtained on the specific MRI machine and on the other, it required adaptation of the stereotactic ring system to MRI compatibility. Furthermore, direct visualization of the distinct nuclei of the basal ganglia system was considered helpful. A series of MRI experiments was performed and a variety of sequences were evaluated using the Siemens Magnetom 1,5T machine. The MRI anatomy of the STN could be defined on a regular basis using specific sequences that were than transferred also onto other machines. However, neither GPI nor VIM could be specifically defined by MRI. In these instances the conventional target coordinates were used, at the same time considering the width of the third ventricle that is easily visualized on MRI. It became obvious [3–5, 7] that this technique is sufficient to define the optimal target for placement of the single permanent quadripolar macroelectrode, when other targeting techniques such as microelectrode recording and stimulation are also applied. These techniques can be used, however, only in an awake and cooperatve patient, while in some patients the surgeon has to rely on the MRI-based targeting techniques alone.

Altogether 179 operations have been performed and a total number of 323 electrodes have been implanted (see Table 3). Although our previous surgical experiences have been reported elsewhere in detail [9, 13], some details have changed so the procedure will be described again in this article. In summary patients who are suffering from side effects of medical treatment of Parkinson's disease or are refractory to treatment for PD or other movement disorders undergo a standard neurological testing including the L-Dopa test. This test is, in our experience as well as in the experience of others, considered to give an optimal estimate of the benefit that the patients may expect from DBS. Exclusion criteria also need to be considered since the surgical procedure is, on one side, a delicate

Table 3. *Patient series with movement disorders Kiel 1999–2004*

	Patients	Electrodes	Target
M. Parkinson	134	231	STN
Tremordominant	4	7	VIM
	3	6	GPI
(essential) tremor	17	32	VIM
Dystonia	18	35	GPI
Myoclonus	2	4	STN
Epilepsy	1	2	STN
Total	179 operations	add. revisions + IPG changes	
	317 electrodes implanted		

procedure requiring full patient cooperation in order to obtain the best results, and, on the other, it is an expensive performance. Therefore it seems mandatory to consider socio-economic factors such as, for example, patient's biological age [16].

As a first step, with the patient in the "off-phase" (without relevant anti-Parkinson-medication) and under general anesthesia using propofol the MRI compatible head ring (3/4 closed ceramic ring; Stryker-Leibinger, Freiburg, Germany) is attached to the patient and an MRI scan is performed using a specially designed series of MRI sequences in order to visualize the sub-thalamic nucleus or another target area and the basal ganglia structures [22]. This is usually performed using the Siemens Magnetom Vision 1,5 T MRI scan (Siemens, Erlangen, Germany). Previously routinely, now only occasionally only a computed tomography (CT) (High Speed Advantage, General Electrics, Milwaukee, MN) scan follows to exclude or to compensate for MRI distortion. Next the optimal target is selected according to the MRI visualization and the stereotactic atlas of Schaltenbrand/Wahren [12]. Early in the series we used the stereotactic software Stereoplan Plus 2.3 (Fa.Stryker-Leibinger, Freiburg, Germany), later SNN 3.14 software (Surgical Navigation Specialists, Mississauga, Ontario, Canada) to plan the optimal trajectory in order to optimize the access via the gray and white matters to and the way through the selected target. The sulci as well as the ventricle structures – which should be avoided – and the three dimensional configuration of the target nucleus are visualized. When the patient is brought back into the operating room (OR), he is awake and ready to be draped, with the Zamorano-Dujovny stereotactic frame (FischerStryker-Leibinger, Freiburg, Germany) attached to the ceramic ring. Usually the dominant left hemisphere is operated on first in order to obtain the best results for the right arm and leg while the patient is still very cooperative and virtually no brain shift has occurred. Under local anesthesia, a skin incision and a burr hole are placed and the needles inserted through the incised dura. Using Benabid's technique with a modified "Ben's gun" (Fischer Stryker-Leibinger, Freiburg, Germany) in most patients five parallel trajectories (see below) are used to insert microelectrodes. Thus, the target nucleus is aimed at and crossed in an optimal manner in order to obtain the most information from microelectrode recording and to select the best site for stimulation. The microelectrode recording is started at least 4 millimeters before reaching the target and continued stepwise through the target. While initially we had used a specially designed apparatus for simultaneous microrecordings (10 MOhm Intraoperative Microelectrode, FHC, Bowdoinham, ME) on five parallel tracks in a distance of 2.3 mm (MEAS, Stryker-Leibinger, Freiburg, Germany) and consecutive 130 Hz microstimulation (Accupulser A310 and Stimulus Isolator A365, World Precision Instruments, Sarasota, FL), in the last patients a Leadpoint-Micromanipulator (Medtronic USA) was used for both microrecording and -stimulation. The microelectrodes are also used to stimulate the targets with continued clinical evaluation of the microstimulation effect. Thereby the optimal site for placing the permanent macroelectrode is selected and subsequently the particular microelectrode track and its depth are used for placing the permanent quadripolar macroelectrode (Medtronic). Two different types of these macroelectrodes (Medtronic, 3389-28 cm resp. 3387-28 cm) are available according to the targeted nucleus – different distances between the poles of the electrodes according to the diameter and length of the nuclei. This macroelectrode is also tested to evaluate the clinical effect of stimulation; when a satisfactory result is achieved the macroelectrode is fixed to the bone with a miniplate after having defined its localization site under fluoroscopic control. At this stage, special attention has to be paid to a "safe" fixation of the electrode cable: not too close to the bone in order to prevent damage to the insulation and not too loose to prevent slippage. In the same way the procedure is carried out on the opposite side. The wound is temporary closed, the patient is brought to stereotactic X-ray and upon confirmation and documentation of the correct locations the patient is taken back into OR to complete the surgical procedure, under general anesthesia, by im-

planting the stimulator, usually Kinetra (Medtronic) and usually in a subclavicular subcutaneous pouch. According to the patient's wishes, the right side is mostly used for insertion of the internal pulse generator (IPG) in order not to interfere with the seat belt crossing the chest when driving car. The stimulator is connected to the electrodes via connecting cables. This part of the operation was in the first patients, performed only the next day, due to time required for the microelectrode recording. With increasing surgical and recording efficacy, this part can be incorporated into the surgical schedule of the same day, so the patient gains an extra day.

Since the entire procedure may provoke "microlesioning effect" altering the basal ganglia circuit similar to the desired effect, the titration of the stimulator is initiated only after one or several days and then tapered according to the clinical symptom of the patients. The day after surgery a MRI scan is performed in order to evaluate the position of the macroelectrodes. Over the next days and prior to completion of the wound healing the patient is transferred to the Neurology Department where the electrical setting of the stimulator is optimized and the medication is reduced according to the specific needs of the patient. Over the ensuing months the patient is followed by a neurologist and a neurosurgeon. The internal pulse generator needs to be exchanged after battery exhaustion after an average of four to six years.

Results

Clinical results

While many centers have already reported short term benefit of DBS in Parkinson's disease and other motor disorders, and only few groups such as Benabid's group [1] have followed patients regularly for a longer period of time in a standardized fashion, our center's experience with a follow up of up to two years has been formally described only recently [8]. Compared to the baseline UPDRS motor score was initially reduced by 50,9% at 6 months postoperatively, and by 57,3% at 2 years follow up. Obviously deep brain stimulation suppresses the major symptoms of Parkinson's disease, it prolongs the "on-phases" and improves the quality of life during both "on and off phases". Thereby it allows reduction of medication to approximately 30–60% of initial medication and also reduces the side effects. Furthermore socioeconomic calculations indicate that, depending on the specific country setting, DBS may reduce the overall cost of treatment for this selected patients group with a defined severity of the disease. These data, however, are presently under study in a national multicenter trial for DBS surgery to STN and need to be confirmed in a longer time setting [16].

Also, very specific items have been evaluated in patients from our series. Data show they may indeed improve after DBS concerning a number of symptoms which may variably influence patients' daily activities.

Gait analysis was carried out in 9 patients with special reference to gait velocity, cadence and stride length [17]. It could be shown that DBS of STN in PD patients improves gait velocity and stride length. While stride length was more improved by suprathreshold dose of L-dopa, cadence was more improved by STN stimulation. In two patients with freezing during the "on phase", STN stimulation failed to reduce this symptom effectively.

Grip force together with hand dyskinesias being one of the important items for daily life activities, these details have been analysed carefully. It could be shown that there is indeed a measureable improvement of both grip force itself and dyskinesias which otherwise may hamper the useful application of the grip force [21]. It has further been shown in this regard, that DBS improves the proximal arm movement even more than fine finger movements [20].

This finding suggests that a combination of both L-dopa and DBS might be required in the long-term treatment of Parkinson's patients and that a close cooperation between neurologists and neurosurgeons is essential in order to improve long-term benefit for the patient.

Since *vegetative symptoms* such as bladder dysfunction may severely disable patients socially, special attention was also paid to detrusor hyperreflexia. It could be shown that STN DBS has indeed a significant and urodynamically recordable effect leading to a normalization of pathologically increased bladder sensibility [14].

Brain shift

Brain shift is considered one of the major objectives against correct placement of the macroelectrode. This is, as mentioned already, the reason why we usually perform the left hemispheric DBS implantation before

the right hemispheric implantation in order to reduce the risk of CSF leakage and brain shift. It could be shown that more than 2/3 (71%) of all macroelectrodes are implanted on the left side in the central trajectory while the rest is evenly distributed throughout the other 4 trajectories. For the right side, however, this figure for the central trajectory is even lower (63%). Therefore we continue to advocate the use of Ben's gun with a number of parallel trajectories, although sometimes reduced because of complications listed below.

Complications

Since deep brain stimulation is a highly sophisticated technique one does not wonder why this technique, even in dedicated centres operating on large series, may carry a significant complication rate. The risks have to be discussed with the patient and his family preoperatively and balanced against the expected benefits in a specific situation with regard to his future life. Early in the series two patients died and their death was related to asphyxia and intracerebral bleeding respectively. It occurred more than one month after surgery and was clearly related to surgery. A right frontal venous lobe infarction was probably due to surgical coagulating a single lobe-draining vein in the burr hole area which had not been visualized preoperatively on MRI scan; thiscaused a massive deterioration of both the functional and the social level of the patient who suffered from a postoperative left sided hemiparesis.

Other complications were minor and without any lasting effect for the patient. Surgery had to be interrupted four times, twice because of epidural and twice because of subdural hematoma; they were resumedn a few months later and performed without any problem and to great benefit for the patient. Furthermore in a total of ten patients material problems occurred i.e. macroelectrode dislocation, scar formation around the extension cables, disconnection of the connector etc. [6]. In two patients seroma in the IPG pouch required repeated punctures.

As mentioned, a postoperative MRI scan is routinely performed on the following day or, if some suspicion has been raised, a CT scan on the same day at the end of surgery. This may show postoperative abnormalities such as small intracerebral hemorrhages around the macroelectrodes. The postoperative intracerebral hemorrhages were symptomatic in 3 patients, resulting in death as mentioned above in one patient, in hemiparesis in the second patient and the symptoms resolved completely in the third patient. The intracranial lesions, shown by MRI, were asymptomatic in 3 patients.

This obviously raises the question whether it is necessary for quality reasons to implant all 5 trajectories on one side as we do according to Benabids technique, thereby exposing the patient to an increased risk of hemorrhage. It needs to be noted however, that despite the logic behind this thought, no such correlation has ever been reported in various series. On the other hand, although we try to implant all 5 microelectrodes simultaneoulsy, we used all 5 microelectrodes only in 247 out of 300 inserted microelectrodes, in the presence of massive brain atrophy which was thought to render the use of all 5 trajectories impossible. In these 53 electrodes, 1 to 4 microelectrodes were used.

In addition to these "surgical" complications, a variety of other symptoms may occur which may have a negative effect on the outcome of this therapy. Since the target area – the STN as small target and the GPI and VIM as relatively large targets – is surrounded by specific structures, side effects of DBS may include speech and posture problems. Besides, psychiatric symptoms may occur which may be transient or long lasting [8].

While complications have to be discussed with the patient and his family preoperatively, they also need to be included into calculating the costs of therapy.

Discussion

The data presented here as well as the results of other groups confirm that DBS provides benefit to a number of papients suffering from movement disorders, predominantly Parkinson's disease. Careful patient selection, meticulous surgery and interdisciplinary management are mandatory in order to obtain the most benefit for the patients. With these prerequisits, DBS surgery will improve quality of life for a longer period of time at a moderate risk of treatment and at acceptable costs.

While these statements are true for the idiopathic movement disorders little has been published with respect to movement disorders of traumatic, metabolic or toxic in origin. In order to correlate trauma and movement disorders it should be known that there has been a significant head trauma and that a certain time interval between trauma and the onset of symptoms

could be defined. The correlation between trauma and the onset of symptoms can be evidenced by an intracerebral lesion on CT, nowadays MRI scan, and possibly also by metabolic changes as shown on FDG-PET. Whether in these cases the surgical therapy helps as it can in patients with idiopathic movement disorders (of degenerative origin) remains to be seen.

A review of the literature should give some information concerning this important question which has, until now, not been addressed particularly well. Najyernouri [10] described in 1985 a 37 year old man who developed Parkinson's disease following a blunt head injury and in whom CT revealed a low density lesion in the substantia nigra. Bhatt *et al.* [2] presented a posttraumatic akinetic-rigid syndrome with positive response to L-Dopa. MRI scan at the time showed a damaged substantia nigra immediately following trauma, however symptoms developed only after one to five month following the injury. Tourejanski *et al.* [19] described a striatal variant of posttraumatic Parkinson's disease in a patient with posttraumatic encephalopathy and defined this to be different from idiopathic Parkinson's disease, as shown by F18 Dopa uptake in the caudate nucleus and the putamen. No surgical therapy was offered to those patients.

In our series we have operated on only one patient with clear posttraumatic Parkinson's disease; no more patients presented to our Neurology department for further neurosurgical evaluation, perhaps because of its rare occurrence despite raised public awareness.

In our series, however, we have operated on patients presenting with movement disorders of other various origin:

- Hypoxia, mostly perinatal
- medication induced – toxic (resulting in tardive dystonia)
- post-stroke (thalamic tremor)
- multiple sclerosis
- heredo-degenerative disease (spino-cerebellar ataxia)

Furthermore, we have recently performed deep brain stimulation in ten PD patients and in three patients with a clinical picture of dystonia who had previously undergone a variety of destructive procedures elsewhere and also in two patients who had undergone fetal cell transplant for Parkinson's disease in Sweden.

Both groups of patients with a defined morphological alteration such as, on the one hand, scar formation from trauma or previous operations and, on the other, patients suffering from disseminated encephalomyelitis could theoretically present an additional risk for surgical complications. Therefore in these patients particular care needs to be focussed on the selection of patients as well as on the trajectory and the optimal targeting. This led to no increased complication rate in these patients when compared to DBS surgery in degenerative disorders, and to impressive clinical improvement similar to that observed in the other patients. Our experience justifies the exploratory use of DBS in this population without medical treatment options, given the relatively low risk of the surgical procedure.

Alternatives

Lesional surgery

Owing to reversibility and variability of a deep brain stimulation as accepted method of choice in our country only seldom there is an indication for destructive neurosurgical procedure. However, this may be sometimes indicated in old patients who are neither able to tolerate the long procedure of microelectrode recordings nor stimulations through the microelectrodes. Furthermore economic considerations in various countries may still play an important role as well as socio-economic situation because of the costs of the implants. *However even these consideredly small targets such as the subthalamic nucleus located in a very sensitive area, particularly when bilateral surgery is required, would lend themselves rather for stimulation procedures than for a destructive therapy*.

Augmentative surgery

DBS remains to be compared with other procedures in the neurosurgical treatment of movement disorders. Early results with fetal cell implants have been encouraging however long term results have been not so positive. Also continuous infusion of nerve growth factors or other neurotrophic substances – which have been proven safe and well-tolerated in phase II trials – still have to undergo successful phase II and phase III trials.

Future developments

They might include improvement of mechanics of DBS armamentarium such as IPG batteries which can

be recharged transcutaneously. More interesting however will be the search for the optimal target point in order to further improve the selectivity of treatment for a variety of symptoms which until now are summarized under the umbrella of distinct movement disorders. Also, on the basis of recent clinical experience and further understanding of pathophysiology of basal ganglia it may also be discussed whether the indication for DBS may be expanded to treat symptoms such as urinary dysfunction.

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Extradural Motor Cortex Stimulation (EMCS) for Parkinson's disease. History and first results by the study group of the Italian neurosurgical society

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Summary

The preliminary results obtained by the Study Group for Treatment of Involuntary Movements by Extradural Motor Cortex Stimulation (EMCS) of the Italian Neurosurgical Society, are reported. The series includes 16 cases of very advanced Parkinson's Disease (PD), aged 46–81; 15 of them were not eligible for Deep Brain Stimulation. Ten cases have been evaluated at 3–30 months after implantation.

Unilateral, sub-threshold extradural motor cortex stimulation (2–8 Volt, 100–400 μsec., 20–120 Hz) by chronically implanted electrodes, relieves, at least partially, but sometime dramatically, the whole spectrum of symptoms of advanced PD. Tremor and rigor bilaterally in all limbs and akinesia are reduced. Standing, gait, motor performance, speech and swallowing are improved. Benefit is marked as far as axial symptoms is concerned. Also the symptoms of Long Term Dopa Syndrome – dyskinesias, motor fluctuations – and other secondary effect of levodopa administration – psychiatric symptoms – are improved. Levodopa dosage may be reduced by 50%. The effect seems persistent and does not fade away with time. Improvement ranged, on the basis of the UPDRS scale, from <25% to 75%. There was only one case of complete failure. Quality of life is markedly improved in patients who were absolutely incapable of walking and unable arise out of chair. After stimulation they could walk, even if assistance was necessary. Improvement was observed also in those with disabling motor fluctuation and dyskinesias which could be abolished.

Keywords: Parkinson's disease; motor cortex stimulation; axial symptoms; long term dopa syndrome.

Introduction

Extradural motor cortex stimulation for treatment of Parkinson's Disease (PD) has been employed, for the first time, at the Neurosurgical Clinic of Torino, directed by the senior author (C.A.P.), in 1998. First results have been reported in various papers and lectures [5–7, 28, 33–35].

The rationale for the procedure is based on clinical and experimental observation.

Extirpation of the motor cortex [2] and section of the corticospinal tract fibres [17, 39] blocks permanently parkinsonian tremor.

In parkinsonian patients single shock stimulation in the posterior limb of the internal capsule gives rise to muscular jerks; high frequency stimulation to tonic muscular contraction in the opposite limbs [31]; high frequency subthreshold stimulation blocks parkinsonian tremor during the stimulation leaving voluntary movement unaffected (Pagni 1963, unpublished data).

Stimulation of the sensory-motor cortex, subthreshold for movement, blocks tremor and rigor in PD; moreover, during stimulation, voluntary movements were unaffected and strength of movement improved [45]. Subthreshold transcranial magnetic motor cortex stimulation improved motor performances in akinetic parkinsonian patients [36].

High frequency extradural motor cortex stimulation, subthreshold for muscular contraction, had been introduced in 1985 by Tsubokawa [42, 43] for treatment of deafferentation pain. The method has been widely employed (see 32). Moreover Katayama *et al.* [19, 20] observed that high frequency motor cortex stimulation reduced, in cases of central pain, associated post-stroke involuntary movements: hemichoreoathetosis; distal resting and/or action tremor

(due to striatal or thalamic infarct); proximal postural tremor (due to midbrain or thalamic infarct or haemorrhage). Improvement of associated hemiparesis was observed in most of those patients.

Abnormal output activity of the basal ganglia nuclei, as shown in non-human primate parkinsonian model, is transmitted to the brainstem and to the cortical brain areas involved in initiation of movement: premotor, motor and supplementary motor area (SMA). This abnormal output activity, disrupting the function of the motor system, (whose areas are underactive in Parkinson's Disease or may present with continuous firing in SMA), is at the basis of symptoms of PD (tremor, rigidity, akinesia, gait and postural disorders) (44, and for a review 22).

In non-human-primate parkinsonian model the internal segment of the globus pallidus and substantia nigra showed increased bursting and increased neuronal firing [22]. Microeletrode recording in the human thalamus, in PD, showed various pattern of abnormal cells firing in the Ventro Lateral thalamic nucleus. Thalamic hyperactivity which follows deafferentation in animal, is inhibited by motor cortex stimulation [43].

All this suggested the possibility that subthreshold motor cortex stimulation, through chronically implanted subdural or extradural electrodes, might help to improve symptoms in Parkinson's disease [36, 45].

In the first few treated cases the method resulted effective for the control of many symptoms of PD (see for a review 35), so that, on behalf of the Italian Neurosurgical Society, a "Study Group for Treatment of Involuntary Movements by Extradural Motor Cortex Stimulation" has been founded in 2002. Members of the Study Group are the following Neurosurgical Departments, whose members participated to the meetings for the elaboration of a study protocol:

Neurosurgical Clinic, University of Ancona
Neurosurgical Clinic, University of Catanzaro
Neurosurgical Clinic, University of Messina
Neurosurgical Clinic, University of Milano-Bicocca
Neurosurgical Clinic, University of Napoli
Neurosurgical Clinic, Catholic University of Roma
Neurosurgical Department, Bellaria Hospital, Bologna
Neurosurgical Department, CTO Hospital, Roma
Neurosurgical Department, City Hospital, Pescara
Neurosurgical Department, Rummo Hospital, Benevento
Neurosurgical Department, City Hospital, Trieste
Neurosurgical Department, City Hospital, Ferrara
Neurosurgical Department, Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)
Neurosurgical Department, Neurological Institute, C. Besta, Milano

According to the protocol for the treatment were eligible: the patients with advanced idiopathic PD who showed a good response to previous levodopa treatment, having a history of at least 5 years, belonging to Hoehn and Yahr III–V degree, showing an UPDRS in off >/=40/108 with motor fluctuations and dyskinesias and the patients who were not eligible for or refusing Deep Brain Stimulation (DBS).

Patients were not eligible if presented: epileptic seizures, psychiatric symptoms (except drug-induced), severe general internal disease, severe cognitive deterioration. [Among early few cases a patient with marked cognitive deterioration was included]

Before, during and after the treatment patients were submitted to: neurological evaluation (UPDRS off/on), psychiatric and neuropsychological evaluation, brain MRI with gadolinium and functional MRI, neurorehabilitative evaluation, EEG, SPECT (99mTc-ECD; 123I-DATSCAN; 123I-IBZM), Bereitschaftpotential P300. A motion picture was recorded before and after treatment.

Material and method

Cases no. 1–6 in Table 1, were previously reported [5–7, 33–35]. The nos. 7–16 have been treated by the Study Group.

Fifteen out 16 patients, 10 males, 5 females, aged 56–81 years, were not eligible for DBS owing to one or more of the following: age; cortical atrophy; cerebral vasculopathy with ischemic foci in the white matter; poor general conditions; slight to moderate dementia; depression; hallucination; leucoencephalopathy; agenesia corporis callosi. One patient, male age 46 (nr. 15 in table nr. 1) had been previously submitted to DBS (bilateral Globus Pallidus; Centre Median and parafascicular nuclei).

ECD SPECT when performed, showed cortical and sub-cortical hypoperfusion.

The patients had been submitted for 6–22 years to medical treatment with levodopa-benserazide, levodopa-carbidopa, pergolide, metixene, pramipexole, cabergoline, amantidine, bromocriptine, selegiline, entacapone.

Three patients rated V at the Hohen Yahr scale; 2 patients rated IV–V; six rated III–IV and 5 rated IV. They presented with the whole spectrum of symptoms of the disease: postural tremor; severe rigidity; trochlea; severe bradykinesia or akinesia; severe limitation of voluntary motility; diffuse cogwheeling; difficulty in rising from a chair, in standing; severe disturbances in initiating the gait; festination; anteropulsion; gait was impossible in six of them, who could try and walk for two-three steps only with assistance; dysphagia, hypo-

Table 1.

Age	Sex	History	Drug therapy	Hoehn Yahr	LongTerm Dopa Syndr.	Other Symptoms	Case nr.
75	F	22 years	Levodopa+carb	IV–V	yes	yes	1
65	F	9 years	Levodopa+bens. Pergolide Selegiline	IV	yes	yes	2
68	M	9 years	Levodopa+carb Entacapone	IV	yes	yes	3
71	M	20 years	Levodopa+carb/bens.Entacapone	V	yes	yes	4
81	M	6 years	Levodopa+carb/bens.Cabergoline	III–IV	yes	yes	5
67	M	11 years	Levodopa+carb/bens.Entacapone	III–IV	yes	yes	6
68	M	10 years	Levodopa+carb/bens.Bromocriptine	III–IV	yes		7
77	M	13 years	Levodopa+carb. Gabaser	V			8
72	M	9 years	Levodopa+carb. Pramipexole	IV–V			9
59	M	6 years	Levodopa+carb	III–IV	yes	yes	10
68	F	10 years	Levodopa+carb	III–IV	yes	yes	11
67	M	9 years	Levodopa+carb	III–IV	yes	yes	12
56	M	17 years	Levodopa+car Pramipexole Amantidine	V	yes	yes	13
70	F	14 years	Levodopa+car Pramipexole Apomorphine	IV	yes	yes	14
46	M	12 years	Levodopa+bens.	IV	yes		15
78	F	22 years	Levodopa+bens.	IV	yes	yes	16

phonia and/or dysarthria and/or poorly intelligible speech; painful focal dystonia; vegetative disturbances.

In some case many of the symptoms were still well controlled by levodopa therapy; but especially those patients who, under levodopa treatment, were still able to stand and walk in a satisfactory manner, with minimal tremor and rigor, presented with invalidating very marked fluctuation of the motor performance (awakening and night akinesia, wearing off effect, on-off phenomena) and choreiform dyskinesia (plus hallucinations and delusion in one case).

Before treatment the score at the UPDRS, off-medication, was 65.5–140; on-medication 38–60.

Three patients affected by Parkinsonism due to Multiple System Atrophy or vascular disease have also been treated. They are not included in Table 1.

In some case the central sulcus was localized (on the hemisphere opposite to the side on which the symptoms begun) by the Taylor-Haughton coordinates. It was marked on the head skin. A plastic tube, filled with paramagnetic fluid was applied over the marked skin. The upper limb motor area was identified by MRI and functional MRI imaging and the location of the paramagnetic marker was adjusted in order to have an overlapping with the motor ascending convolution, whose localization was marked on the skin. In other cases MRI images were transferred to the patients with the help of the neuronavigator.

Under general or local anaesthesia, through two burr holes or a small craniotomy over the upper limb area, a quadripolar electrode (model 3587A, Medtronic, Inc., Minneapolis, USA) was introduced in the extradural space, over the motor area (fig. 1). According to the protocol of the Study Group the exact localization of the motor area is obtained by recording of the Evoked Sensory Potential (phase reversal N20/P20 in front and behind the central sulcus) or by recording of the EMG responses in upper limb by suprathreshold motor cortex stimulation.

The electrode is connected to an external electrostimulator.

During 10–14 days stimulation test, with current subthreshold values for movement, various parameters (2–8 Volt, 100–400 μsec., 20–120 Hz) and several setting of the active electrodes, was performed. Benefits were seen with many combinations of parameters and electrode setting. Best results were obtained with 2.5–6 Volt, 150–180 μsec., 25–40 Hz. The electrode was then connected to an implanted electrostimulator (Medtronic ITREL II) at the most efficacious stimulation range. Stimulation may be delivered throughout the day and stopped during the night, or delivered during night and day.

Results

Out of 16 cases 3 have been implanted less than two months ago and they have not been finally evaluated yet. In one case (nr. 13), who showed clear improvement, stimulation was stopped owing to general disease. It was resumed again, but a complete evaluation is presently still impossible. In one case (nr. 7) there was no improvement. The stimulator was removed 4 months later because of skin necrosis.

One case deserves special emphasis (nr. 15). This patient had been submitted to bilateral implantation on the Globus Pallidus and on the Centre Median

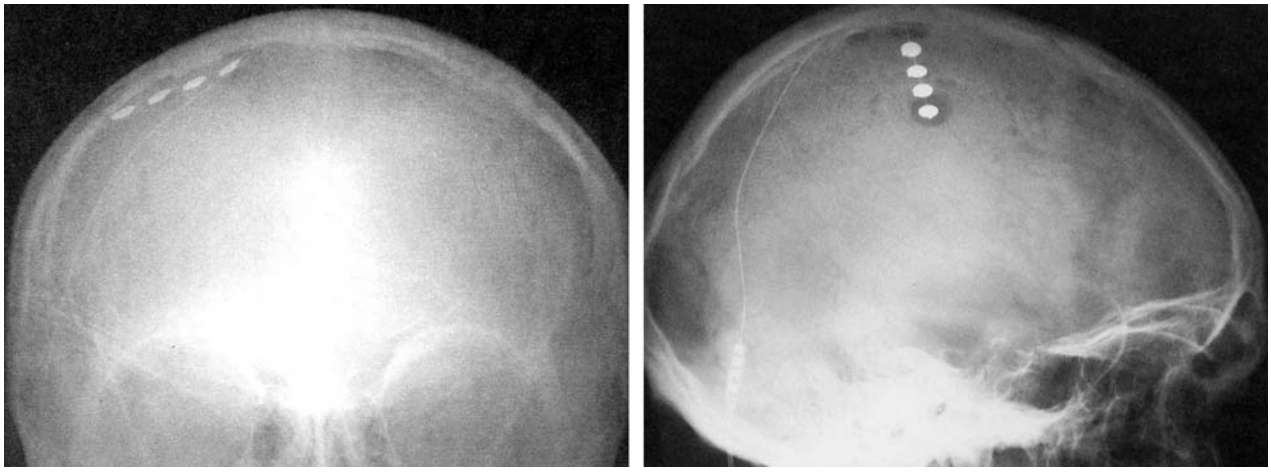

Fig. 1. Skull radiographs showing the electrodes in place

(CM) and parafascicularis: bilateral or unilateral DBS of the CM gave an excellent result with an improvement of more than 75%. Owing to infection one deep electrode was removed, and the patient submitted to unilateral Extradural Motor Cortex Stimulation for one month. The result was identical to the result of DBS, that is with an improvement of more than 75%. Now DBS has been resumed with great benefit and the patients is under study (dr.P.Mazzone, Roma).

More or less marked benefits, which in some instances look dramatic and seem to be permanent, were observed in 10 out of 16 cases. The benefits were the following:

a. abolition or striking reduction of tremor and rigor in all four limbs; the effect was more marked in the limbs opposite to the stimulated side;
b. cogwheel reduction;
c. striking improvement of bradikinesia and akinesia;
d. marked improvement of postural stability, standing and gait; patients who could not walk at all can walk without or with minimal assistance, even if posture was still slightly camptocormic; patients can walk independently for more or less long distance, change quickly direction, climb the stairs; festination is reduced or nearly completely abolished;
e. marked improvement of motor performance, also of skilled motor function;
f. dysphagia improved; speech improved: dysarthria is reduced and speech is more intelligible; improvement of facial expression
g. control of the Long Term Dopa Syndrome (nocturnal akinesia, wearing off and on-off symptoms, choreiform dyskinesia). In one case hallucinations also disappeared;
h. levodopa and other drugs could be gradually reduced by 30–50%.

This is an exemplary case.

71 yrs, male, 20 years of history, treated with levodopa+carbidopa 700 mg/day, levodopa+ benserazide 275 mg/day, entacapone 400 mg/day since 20 yrs.

On-therapy his voluntary motility was severely incapacitated, he was absolutely unable to get up by himself, stand and walk and presented with nearly continuous choreiform movements of the face, neck, trunk and limbs. Speech was monotone, slurred; masked face. Tremor and action postural tremor were slight to moderate. Rigidity was practically absent. Finger taps, hand movements, alternating movements of hands and leg agility were impaired. Rising from the chair, standing and posture, gait was absolutely impossible.

Before stimulation the UPDRS scores Part III-Motor examination, and Part IV-Complication of therapy, on-medication, were 31 + 14 = 45. The score of Part III items 23/29, on medication, was 24.

After stimulation there was a dramatic improvement of UPDRS items 23/29 of Part III which decreased from 24 to 9: the patient was able to rise from a chair, to stand alone and walk, in spite of camptocormic posture and not perfect balance. Also complications of treatment were dramatically improved. Levodopa dosage was reduced by 35%. The choreiform movement were abolished. Owing to that the score of Part III and Part IV decreased from 31 + 14 = 45 to 15 + 6 = 21.

The follow-up of this patient was only 5 months, because he died suddenly owing to an acute abdominal haemorrhage.

On the contrary relief from symptoms was practically nil in two cases of Multiple System Atrophy. However Mazzone observed a slow progressive improvement in one patient affected by vascular parkinsonism with dystonia submitted to bilateral implantation (unpublished data).

No complications due to the surgical manoeuvres and stimulation were on record. Epileptic seizures due to prolonged high intensity stimulation performed during implantation, to evoke muscular jerks in the opposite limbs, were observed in one case. But subthreshold stimulation did never evoke seizures due to kindling.

In one patient (case nr. 7) there was cutaneous necrosis over the stimulator which was removed. It has been reported [7] that one patient [not included in this series owing to lack of information] who had previously suffered from depression and psychiatric disturbances, experienced hallucinations requiring therapy, six months after implantation in the right hemisphere.

Discussion

In this preliminary experience EMCS has been employed in patients with very advanced PD, in poor conditions and/or with cerebral atrophy and/or cerebral vasculopathy. Clinical evaluation was possible in 10 cases at 3–30 months follow-up. The method seems to afford satisfactory relief not only from tremor and rigor but also from other symptoms of advanced PD [34, 35] and especially from some axial symptoms, as disturbances of posture, gait and rising from chair; body bradykinesia and facial hypomimia. Also impairment of hands and legs movements may be improved as far as opening and closing hands, pronation-supination, spreading of the fingers and use of the hand is concerned. Results seem to be persistent, the follow-up having been nearly 3 years in the first reported case [7].

Special emphasis deserves the fact that complications of levodopa therapy, motor fluctuation and dyskinesias, were dramatically improved or abolished, perhaps owing to the reduction of the levodopa dosage [33].

Result and grade of relief seems unpredictable. One patient (case 7) did not present any improvement; in 3 cases the improvement was rated $< 25\%$; in 6 cases 25–50%; in 1 case 50–75%. [Case nr. 15 is not included owing to the short period of stimulation – one month].

In spite of the fact that global rating of the success, in patients so severely disabled, might seem to be rather low [in most of the cases it was 25–50%], life quality was dramatically improved owing to abolition of disabling dyskinesias and improvement of axial symptoms [walking, falling, swallowing, etc.], so that assistance was made easier. Thus rating of the success by the family was always higher than rating based on the UPDRS and medical staff evaluation.

Mechanism underlying those results is not clear. No doubt cortical stimulation with the electrodes and the parameters employed activate large cortical areas, millions of nerve cells and fibers, and very diffuse complex systems of interneurons [37].

Rigidity and bradykinesia might be due to hyperactivity of disinhibited sensory motor cortex [18, 38]. The Torino experience in patients affected by central pain syndromes [4, 32] suggests motor cortex stimulation increases the cortical GABA. Sub-threshold motor cortex stimulation might thus reduce cortical hyperactivity increasing GABA concentration.

According to others, bradykinesia and rigidity might be due to abnormal prolonged firing of preparatory movement set SMA cells, causing disruption of the neuronal activity of movement related cortical motor area cells [44]. Sub-threshold motor cortex stimulation do not activates cortico-spinal cells and fibers, but with the employed parameters [short pulse width, up to 120 Hz] might activate myelinated axons connecting the motor area to the SMA (both orthodromically or antidromically) thus rebalancing the disrupted SMA activiy.

Another hypothesis, supported by functional imaging studies, is that premotor cortex and supplementary motor cortex are underactive in PD [15], and that improvement of symptoms of PD obtained with stimulation of the Globus Pallidus internus is related to the increase of regional metabolism and regional blood flow in that areas. The Subthalamic Nucleus (STN) in PD is "disinhibited", and thus further inhibits the VL thalamus reducing its excitatory input to the cortex, thus eventually leading to the development of parkinsonian symptoms [41]. The subthreshold motor cortex stimulation might activate the cortico-striatal glutamatergic connections and the loop cortex-striatum-lateral Globus Pallidus, which projects to the STN. Activation of that loop by modulating the

activity of the STN, might rebalance STN influence on the VL thalamus restoring thalamic excitatory input to the cortex.

Moreover, it has been demonstrated that primary motor area (M1) and SMA are directly connected with the subthalamic nucleus [26] and that the corticosubthalamic pathway stems out directly from the pyramidal tract [16]. Thus the corticosubthalamic pathway provides an alternative input to the basal ganglia in parallel with the corticostriatal pathway [40]. It may be that the motor cortex stimulation activates this loop and the STN, thus mimicking the effect of direct stimulation of the STN obtained with DBS (see 22). Worth noting is that the stimulation of the globus pallidus [12] and STN [21] induces changes of cortical motor area activity during alleviation of parkinsonian symptoms.

Cortical stimulation in motor areas may perhaps activate also the "suppressor cortical circuit" and mechanisms [14, 24] whose reduced activity might be at the origin of involuntary movements (see 2).

Bilateral benefit from unilateral stimulation may be explained by many pathophysiological data. Unilateral corticospinal tract interruption in the mesencephalon abolishes dyskinesias in the contralateral limbs and reduces involuntary movements also in the ispilateral limbs [23]. Inhibitory and excitatory interhemispheric transfer via the corpus callosum has been observed in normal humans [25] and in cases of stimulus sensitive mioclonus [29, 30]. Interhemispheric transfer of plasticity is possible too [3]. The motor area and corticospinal pathways are implicated in the ipsilateral movements too [1, 8] and this is quite evident in pathological situations [9–11, 23, 27]. Primary motor cortex is involved in bimanual coordination [13].

What is most important is that levodopa administration may be considerably reduced in some cases (up to 50%) and that Long Term Dopa Syndrome, as well as other symptoms due to levodopa administration (hallucinations), are abolished with great improvement of motor performance and life quality. Abolition of choreic movement of Long Term Dopa Syndrome may be due both to reduction of the levodopa administration and direct effect of cortical simulation (see 20).

While in certain patients affected by neuropathic pain the benefit of motor cortex stimulation fades away with time, this might not be the case for parkinsonian symptoms, whose benefit seems to persist. In one patient, five months after implantation, direct injury resulted in system failure. Clinical worsening began roughly 4 days later, with increasing worsening of the gait and postural stability over the weeks. The system was replaced: the benefit appeared again as at the time of the first implantation (see 5). The observed persistent benefit after system failure might be due to plastic modification of the central neural circuits: if this is the case early employment of cortical stimulation could slow down the progress of the Parkinson's disease.

The presentation of the paper was completed by a motion picture of 5 cases, before and after stimulation.

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Endocrine dysfunction following traumatic brain injury: mechanisms, pathophysiology and clinical correlations

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Summary

Despite growing recognition among those who provide care for traumatic brain injury patients, endocrine dysfunction following brain injury is an often under-recognized phenomenon. From historical reports one would conclude that endocrine dysfunctions hardly ever occurs following trauma to the head. However, recent studies suggest that a significant proportion of patients suffer some degree of hypopituitarism.

To date, there are no clear predicting factors identifying patients at risk for developing hormonal disturbances and thus no parameters exist for screening. Several retrospective analyses and literature reviews, and more recently, a few longitudinal studies of brain injured patients have been performed.

Keywords: Traumatic brain injury; endocrine dysfunction; hypopituitarism.

Introduction

This paper reviews the mechanisms by which trauma can result in pituitary dysfunction. The anatomy and pathophysiology of the pituitary gland during the acute phase of injury and subsequent recovery is also discussed. Mechanisms and pathophysiology of pituitary injury are then clinically correlated through a review of our cases, and those of other groups.

We conclude that testing for endocrinological dysfunction should at least be considered in patients who survive a severe head injury.

Historical perspective

While an association between head injury and diabetes insipidus has been reported by Kahler [15] as early as 1886, post-traumatic anterior hypopituitarism was first noted by Cyran [8] in 1918. The hypopituitary syndrome was called Simmonds disease after Morris Simmonds [30] who described a patient in 1914. In 1942, Escamilla and Lisser [13] reviewed 595 cases of Simmonds disease and found only one allegedly due to trauma; four other cases were taken from the literature. Reviewing the literature in 1961, Altman and Pruzansky [3] collected 15 cases of post-traumatic hypopituitarism and in 1986 Edwards and Clark [12] brought this number up to 54 cases. In 1999, Benvenga *et al.* [4] found a total of 367 cases of post traumatic hypopituitarism in the published literature, including 15 from among their own patients. They further noted that endocrine dysfunction can occur more than ten years after the initial injury, and that the injury may not have been substantial enough to require hospitalization or even be remembered by the patient.

Once post-traumatic hypopituitarism was no longer a reportable rarity, clinicians began to screen for it among their injured patients (Table 1). Cernak *et al.* [7] in 1999 studied 18 patients after direct and indirect neurotrauma during their first week after the injury and found thyroid, gonadal, and adrenal dysfunction compared to other non-brain injured controls. In 2000 Kelly *et al.* [19] studied 22 head-injured patients at a median of 22 months after injury and found that eight of them had a subnormal response in at least one hormonal axis compared to normal healthy volunteers. Lieberman *et al.* [22] found neuroendocrine dysfunction in 68% of 70 patients at a mean of 49 months after injury. More recently, Dimopolou *et al.* [10] have found hormonal dysfunction in 18 of 34 patients evaluated after ventilator weaning following brain injury, and Agha *et al.* [1] have found numerous anterior and posterior pituitary dysfunctions among 50 patients at a median of 12 days following brain injury.

Collectively, these studies have revealed that just as the spectrum of endocrine dysfunction after injury

Table 1. *Longtitudinal studies of hormonal disturbances following non-penetrating traumatic brain injury*

Reference	Time point	n	GH axis	Sexual steroids	Corticotrophic axis	Thyrotrophic axis	Prolactin	Hypopituitarism	D. I.
Bock *et al.* [5]	7 days	27	1	m 15/18	7	14	–	9/27	–
Cernak *et al.* [7]	7 days	8	–	*	*	*	–	*	–
Agha *et al.* [1]	12 days	50	9	40	8	1	26	–	13
De Marinis *et al.* [9]	16 days	21	*	–	–	–	*	*	–
Dimopoulou *et al.* [10]	22 days	34	3	8	8	5	–	18/34	–
Nomikos *et al.* [23]+	3 mos.	11	2/6	0	3	4	3	5/11	8
Schneider *et al.* [28]	3 mos.	26	3/25	12/25	5	–	–	23/26	–
Lieberman *et al.* [22]	13 mos.	70	7/48	1/60	5/70	15/69	–	48/70	–
Kelly *et al.* [19]	26 mos.	22	4	5	1	1	–	8/22	–
Richard *et al.* [27]	–	93	–	17/6	0	1/93	–	27/93	–

Time point reflects either the median time point after injury at which patients were tested, or the duration of the study if all patients were tested at the same time.
* In this study, average values including all patients rather than individual patient numbers were reported, +study included only patients with sellar fractures, –information was not apparent from data.

ranges from diabetes insipidus and Simmonds syndrome to subtleties of dysfunction that can only be elicited by comprehensive hormonal axis testing, so does the mechanism of injury range from frank pituitary avulsion or sellar fracture to milder cortical injury distal from the pituitary. The time frames of both injury and subsequent recovery also remain similarly complex. Further complicating the matter, brain injured patients often suffer from co-existing systemic problems both directly and indirectly related to their initial injuries that can have additional endocrine effect [1, 3, 4, 7, 8, 10, 12, 13, 15, 19, 22, 30].

Mechanisms and pathophysiology of injury

Brain injury resulting in endocrine dysfunction can be divided into direct trauma to the pituitary or its stalk, and indirect trauma to other parts of the brain resulting in hypoxia, cerebral oedema, seizures, and intracranial haemorrhage.

Blunt closed head injury is a more frequent cause of direct trauma to the pituitary than penetrating injury and is thought to result in chronic degeneration of the pituitary end organ axis [7]. The bony encasement of the pituitary within the sella turcica and anastomotic blood supply are protective from trauma, however its interconnection with the basal hypothalamus and infundibulum render it delicate and vulnerable. Morphologically detectable lesions of the pituitary-hypothalamic system such as ischaemic necrosis and haemorrhage occur at an incidence between 43 and 62% after fatal brain trauma [6, 21]. The most frequent site of haemorrhage is the tuber cinereum. Autopsy findings in brain injured patients reveal a normal pituitary in 14 to 74% of cases, haemorrhage, fibrosis or thrombosis of the peripituitary or capsule in 23 to 59% of cases, and stalk necrosis (6%) or haemorrhage in 10 to 27% of cases. The anterior lobe of the pituitary shows haemorrhage in 10 to 27% of cases, necrosis in 13 to 22%, and fibrosis in 5%. The incidence of haemorrhage or necrosis in the posterior lobe of the pituitary ranges from 13 to 42% [6, 21].

The blood supply to most of the anterior pituitary lobe, and particularly the areas containing the somatotropic and gonadotropic cells, runs via the long portal vessels which originate above the diaphragma sellae. Additional blood supply to the corticotropic cells of the anterior pituitary is via the short portal vessels. Pathological studies demonstrate that anterior pituitary necrosis occurs mainly in the areas supplied by the long portal vessels, rendering somatotropic and gonadotropic cells more vulnerable to mechanical strain [28].

Fractures of the sella turcica after fatal brain injury are found on autopsy in between one and 20% of cases, depending on whether the petrous temporal bone is included in statistics. Ortega and Longridge [24] in 1974 reported that 48 cases out of 248 autopsies after head injury revealed fractures through the petrous temporal bones and the sella. Dublin and Poirier [11] in 1976 found that the incidence of sellar fractures among 350 cases of skull fracture was 1.4%; they further classified these fractures into three types. Young *et al.* [32] in 1980 divided five sellar fractures into five

Table 2. *Patients with sellar fractures: an overview of pertinent literature*

Referecnce	Year	Cases	Endocrine deficiences
Reverchon *et al.* [26]	1921	1	1
Altman *et al.* [3]	1961	1	1
Dublin *et al.* [11]	1976	5	1
Kanade *et al.* [16]	1978	1	1
Pere *et al.* [25]	1980	1	1
Young *et al.* [32]	1980	5	4
Gomez-Saez *et al.* [14]	1982	1	1
Kojima *et al.* [20]	1985	3	0
Keeling *et al.* [18]	1986	3	2
Edwards *et al.* [12]	1986	1	1
West *et al.* [31]	1993	40	4
Kawai *et al.* [17]	1995	1	1
Kelly *et al.* [19]	2000	1	1
Segal-Liebermann *et al.* [29]	2000	1	1
Nomikos *et al.* [23]	2003	11	5

different types. In 1985, Kojima *et al.* [20] reported the incidence of fractures of the sella turcica as 1% (3 of 282 head injuries patients). West *et al.* [31] examined 40 autopsy cases after injury and found that transsphenoidal basilar skull fractures can be divided into four major patterns of fracture along planes of weakness in the bone: anterior transverse (55%), posterior transverse (40%), lateral frontal diagonal (17%) and mastoid diagonal (7%). Eight patients (20%) had two fracture patterns.

Patients with fractures of the sella turcica have pituitary injuries ranging in severity from gross lesions to smaller haemorrhages (Table 2). Infarction, stalk resection, and lesions in the hypothalamus and optic chiasm can be visualized with dedicated MRI scans.

CT or MRI in 76 patients with postraumatic pituitary insufficiency revealed normal sellae in 7%, haemorrhage of the hypothalamus in 29%, haemorrhage of the posterior lobe of the pituitary in 26%, infarction of the anterior pituitary lobe in 25%, stalk resection in 4% and posterior pituitary infarction in 1% [4].

Indirect trauma to parts of the brain excluding the sellar region, can also result in endocrine dysfunction. Differentiating central endocrine dysfunction due to brain injury from endocrine dysfunction due to systemic causes may be possible with careful testing of the hormonal axes particularly after the acute phase of trauma has subsided. Prolonged critical illness is associated with general suppression of the somatotropic system rather than growth hormone (GH) resistance. Schneider *et al.* have shown that there is no GH response to GHRH stimulation in cells taken from non-surviving patients after TBI [28]. The thyrotropic axis displays reduced peripheral T_4 conversion in the acute phase after trauma. Depressed thyroid hormone levels after TBI are associated with poor outcome. Deficiencies of the hypothalamic-pituitary-gonadal axis in the acute phase after trauma reveal low gonadotropins, low testosterone levels and high LH levels. There seems to be a correlation between the decrease in testosterone levels and the severity of TBI. The acute phase of critical illness is generally associated with increases in ACTH and cortisol levels, although ACTH elevations are frequently less pronounced after TBI than they are in other, comparable types of critical illness. The occurrence of relative hypocortisolism may muddle the clinical picture because this usually suggests a systemic problem and it is unclear if these numbers need to be treated during the acute phase of recovery from trauma.

Studies by Kelly *et al.* [19] have shown that somatotropic and gonadotrophic deficiencies occur most frequently after TBI. Lieberman *et al.*'s [22] data revealed 31% of patients without abnormalities, 51% with a single abnormal axis, (26 adrenal, 8 thyroid and 2 GH) and 17% with dual abnormalities after TBI.

A case series from our group [23] described the endocrinological findings of 11 TBI patients with skull base fractures involving the sella turcica. The basal levels of anterior pituitary hormones, their response to ACTH, TRH and LHRH stimulation, plasma electrolytes and osmolality and daily urine output were measured. Polytrauma was present in 8 of 11 patients, initial coma in 7 of 11, cranial nerves lesions in 7 of 11, and palsies of the extremities in 5 of 11. Prolactin was elevated in 3 patients and was low with an absent response to TRH in one case. Growth hormone could not be stimulated in 4 cases and the cortisol response to ACTH stimulation was subnormal in 4 cases. Hypogonadism with subnormal stimulation of LH and FSH was present in 3 cases. Only one patient was found to have hypothyroidism. Diabetes insipidus was present in 8 patients. Endocrinological data 2–4 months after injury were available in 8 patients (1 died, 2 were lost to follow-up). Recovery of pituitary function was noted in 2 of the 3 patients with initial impairment of adrenal function. One of the patients with hypogonadism recovered. Diabetes insipidus was transient in 6 of 8 cases.

A second series from our group [5] investigated acute hormonal changes and early parameters pre-

dictive for hypopituitarism after TBI. A total of 27 patients hospitalized for head injury were screened for endocrine deficiencies zero, 3 and 7 days following head injuries. Results showed that basal hormone measurements on day 7 of hospitalization indicated disturbances of the corticotroph axis in 26% and 7% of patients if cut-off levels of 10 μg/dl and 5 μg/dl respectively are utilized. TSH levels ranged between 0.01 and 7.9 mU/l with fT4 of 0.6 to 1.7 ng/ml. Three patients had GH levels > 5 ng/ml whereas 11 had levels < 1 ng/ml. Age adjusted IGF-1 was subnormal in 4 patients on admission, however, on day 7 only 1 patient had a subnormal IGF-1 level. Fifteen of 18 male patients had subnormal serum testosterone levels. Eight subjects had LH concentrations < 1 U/l. Evidence of hypopituitarism was detected in 34% of patients.

Clinical correlations

Patients with risk factors for hypopituitarism include those with diffuse cerebral oedema or hypoxia, preceding hypotension, moderate or severe TBI, and basal skull fracture [19]. Patients with mild TBI should also be tested if they exhibit symptoms of hypopituitarism. Unless patients have radiographic apparent sellar injury or diabetes insipidus, testing during the acute phase of trauma may not be helpful. Endocrine alterations at this time are generally transient and may be due to critical illness, rendering them difficult to interpret and treat [4, 12, 22]. The frequent presence of hypopituitarism and necessity for immediate replacement therapy in the event of corticotropin or thyrotropin deficiency suggest that testing during the subacute (at 3 months) and chronic (9 to 12 months) phase of trauma rehabilitation may be judicious. Additional testing may be mandated by clinical findings.

Deficiencies of the thyroid, gonadotropic and, with some restrictions, corticotropic axes, can in most cases be diagnosed by measuring basal hormone levels. Growth hormone deficiency requires stimulation tests for diagnosis because in many cases normal IGF-1 levels do not exclude GH deficiency [2]. Nonetheless, IGF-1 is a useful predictor of GH deficiency in patients who have risk factors for hypopituitarism but do not exhibit malnutrition.

Basal serum hormone concentrations that should be determined include morning cortisol, free T_3 and T_4, TSH, testosterone/oestradiol, LH, FSH, prolactin and IGF-1. In this context, it is important to record any problems relating to the menstrual cycle, libido or sexual functioning. Furthermore ACTH should be tested in suspected cases of corticotroph deficiency when patients have low or low normal cortisol levels, hypotension, and/or fatigue. When IGF-1 levels are low and/or other axes are impaired, the somatotrophic axis may be assessed by the GHRH-arginine test [2].

Replacement of hydrocortisone and L-thyroxine in patients with deficiencies should be instituted immediately. Testosterone, estrogen and growth hormone deficiencies often require treatment under particular patient circumstances.

Conclusions

The prevalence of pituitary insufficiency after TBI may be as high as 30–50% among survivors. These figures suggest an alarming socio-economic impact. Conservative estimates would suggest approximately 5000 newly acquired cases of pituitary insufficiency from trauma in Germany. A substantial percentage of these patients probably remained undiagnosed and untreated.

Currently, there is an urgent need for longitudinal studies to provide information on the degree to which pituitary deficiencies are transient or persistent and to define further the risk factors resulting in pituitary dysfunction.

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Taylored implants for alloplastic cranioplasty – clinical and surgical considerations

B. Hoffmann and **A. Sepehrnia**

Summary

Traumatic loss of bone substance or post – decompression defects require the reconstruction of the skull. In cases of simple geometry there are handy, secure and cost effective procedures such as using autologuous cryopreserved bone flaps or polymerized Methylmethacrylat. For large sized defects CAD – taylored implants developed to provide a comfortable procedure to ensure high biocompatibility and perfect anatomical results by one – stage surgery. Furthermore cranioplasty does not only imply anatomical reconstruction but also functional recovery of awareness, cognition and motoric functions as shown in several studies according to changes in cerebral hemodynamics and metabolism. In our series of 286 patients who underwent cranioplasty during the past 10 years (1993–2003) we used taylored implants in 15 cases starting in 1999. All the patients included showed large sized defects > 64 cm^2, complications did not occur neither during surgery nor the postoperative course, cosmetical results were excellent in all the patients. Neurological findings and the functional state improved in 11/15 patients, 4/15 patients showed no change, nevertheless these patients had reached a good recovery before surgery. Application of this technique is limited by cost, nonetheless it is recommended for extensive reconstruction of the skull.

Keywords: Cranioplasty; CAD; taylored implants; titan; activities of daily life.

Introduction

Traumatic loss of bone substance, large defects after decompression hemicraniectomy or resection of extensive tumors involving the skull base require reconstruction techniques which should be easy to apply for the surgeon, safe for the patient and cost effective, respecting the economical resources of the public health system. Main issues of surgery are cosmetic but also functional considerations according to reports in the literature [4, 7, 8, 10, 12] that outline the importance of compromised cerebral hemodynamics and metabolism in post – craniectomy state as well as clinically and measurable improvements after cranioplasty. Quite common surgical procedures are reimplantation of cryo-preserved bone flaps and the use of Polymethylmetacrylat (PMMA) that are known to ensure good results in most of the patients [1, 13]. For large defects and geometrically complex situations, especially in cases of involvement of the craniofacial skeleton, taylored implants had been introduced as prefabricated alloplastic grafts which are precisely formed before surgery using high resolution 3D CAT scans and CAD/CAM techniques [2, 3, 5, 6, 9, 11]. All surgeons agree that this technique provides precise planning of surgery with high grades of biocompatibility and mechanical properties. We want to discuss a consecutive series of 15 patients with large defects > 64 cm^2 operated in our department to reflect the surgical results as well as the functional outcomes.

Materials and methods

During the past 10 years (1993–2003) 286 patients underwent cranioplasty in our department.* Fifteen patients were selected for surgery using taylored implants, starting in 1999. Eight patients were male, 7 female with an age range from 21–65 years (Mean 33 years). All the patients suffered from the sequelae of severe head injuries with bony defects of >64 cm^2, affecting the frontal bone bilaterally in 5 cases, the frontal calvaria unilaterally including the orbital roof in 3 cases, the fronto – parieto – temporal region with involvement of the orbit in 4 cases and without in 3 cases. The size range of the defects to reconstruct was 64–225 cm^2 (mean 121 cm^2). In 2 of the cases we decided for a taylored implant after failure of cranioplasty with a cryo-preserved bone flap due to aseptic bone necrosis. During the stay in the hospital all the patients underwent our early rehabilitation program with intense neuropsychological training, speech therapy, ergotherapy, physiotherapy and activating nursing for at least 8 hours a day. All the patients in this group were free of severe co-morbidity and did not suffer from recent infections. Bacterial colonisation and potentially multi-resistant dangerous bacteria were excluded. Standard CAT scans ensured that there was no evidence of compromised CSF circulation. CAT data acquisition was performed by a spiral CAT scan, using a short spiral with a collimation of 1 mm, the gantry tilt was adjusted to 0°. The increment of reconstruction amounted 1 mm, a linear interpolation algorithm of 180° was used. The taylored implants were manufactured by C+P (Center for Prototyping), Erkelenz, Germany. Based upon the digital CAT

* Former head Prof. Dr. K. von Wild, 1982–2002.

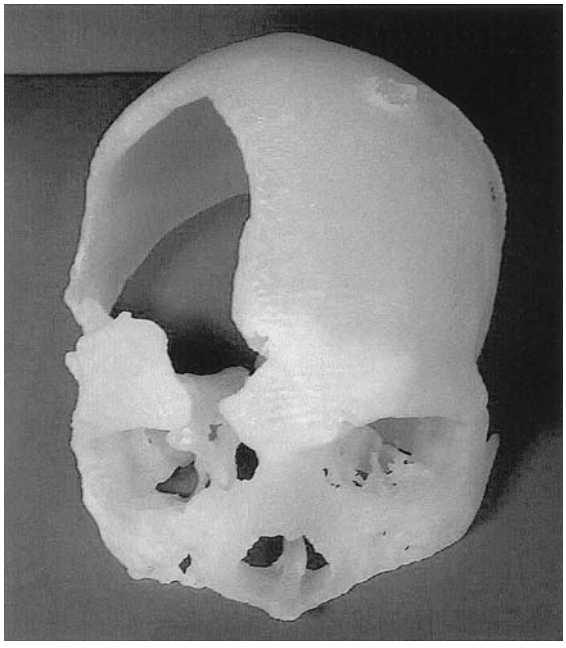

Fig. 1. Stereolithographical model of a patient's skull after severe head injury showing the large bone defect including parts of the orbital roof

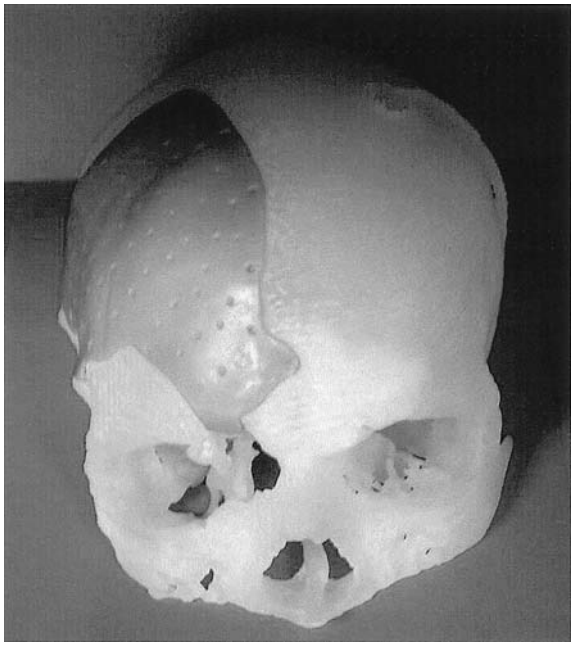

Fig. 2. Stereolithographical model of the skull of the same patient as Fig. 1; wax pattern in situ

data a stereolithographic model of the skull was generated (Fig. 1) and a wax pattern was formed to cover the bony defect (Fig. 2). This wax pattern served as a template to fabricate the titanium implant in a molding procedure. Surgery was performed from 48 to 125 days after trauma (mean 72 days). During surgery the implants (Fig. 3) were fixed by Leibinger 1.7 mm screws (length 7 mm). After surgery

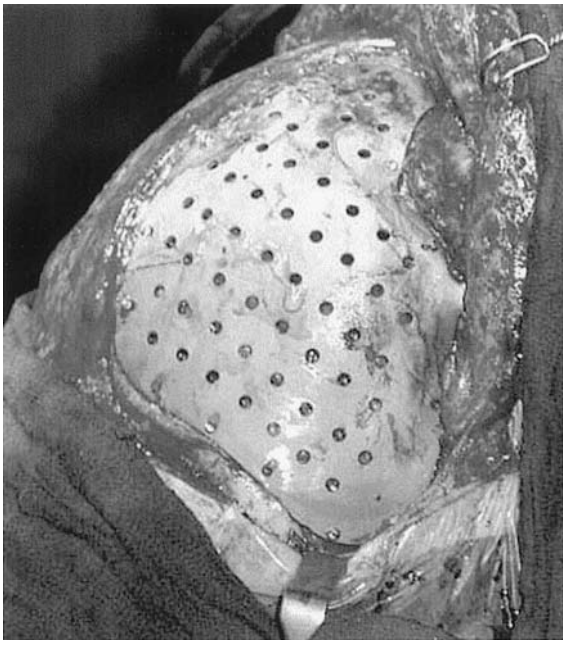

Fig. 3. Same patient as Figs. 1 + 2 showing the titan taylored implant after fixation by Leibinger Screws

a standard CAT scan was performed to exclude intracranial pathology and a 3D scan documented the surgical results. The clinical findings and patients' competence in activities of daily life were investigated once a week during hospital rehabilitation and 6 months after discharge from our department.

Results

All of the implants fitted perfectly according to the preoperative virtual planning and the wax pattern template. No corrections during surgery were necessary. The time range in the operating theatre was 60–132 minutes (mean 102 minutes) with times for surgery itself from 45–102 minutes (mean 88 minutes). Due to careful preparation of the large galea flaps intraoperative blood loss was 250–650 ml (mean 385 ml). Anaesthesiological problems did not occur, neither during surgery nor in the postoperative course. The lowest hemoglobin value after surgery was 9.7 g/dl due to colloid infusion and following hemodilution. Subgaleal drainage remained for at least 2 days with a postoperative blood loss of 120–180 ml (mean 134 ml), none of the patients needed transfusion of red blood cells neither during surgery nor during the postoperative course. The cosmetic results were excellent in all of the cases, the postoperative CAT scans showed no intracranial pathology and no irregularities of the implants compared with the preoperative simulation.

In our series we did not observe any complications such as infection, epi or subdural effusions, hematoma or dislocation of the implant, no corrective surgery was necessary. The CAT investigations after 6 months did not show any pathology due to surgery. The clinical findings and the functional state improved in 11/15 patients, 4/15 patients showed no change of their state respecting that these 4 patients had reached a good state of recovery before surgery. We did not observe cases of deterioration in awareness, cognitive or motor dysfunction, 1 patient suffered from primary generalized seizures with a known preoperative history, in 1 case with focal seizures and difficulties in preoperative medication no more ictus was observed in the postoperative course. The Functional independence measure (FIM) score improved in 11/15 patients between 15–45% (mean 25%) during the first 6 weeks after surgery. The 6 months controls showed no complications due to surgery, the functional state continued to improve in 7/15 patients with consolidated results in the rest of the group.

Discussion

Preoperatively manufactured CAD/CAM implants from titanium proved to be a handy and secure technique to reconstruct large cranial bone defects. In our series we can confirm good results of other groups [5, 6] concerning a precise anatomical reconstruction of the calvaria and the craniofacial sceleton. The preoperative efforts for planning, data acquisition, digital reconstruction and manufacturing are comparable to a short time for surgery and also short and effective use of capacities in the operation theatre. As well as from cosmetic reasons the patient benefits from low risk surgery with immediate postoperative mobilization and possibility to continue his rehabilitation program without stress due to postoperative morbidity. We can also confirm the empirical reports about clinical improvement after cranioplasty, which should have an even bigger importance in extremely large cranial defects [8, 10, 12]. Nevertheless the clinical improvements require an existing rehabilitation potential and still working CNS plasticity as well as an intense treatment of the patient by specialized team. We prefer early surgery in all of the cases, which requires a stable state of the patients without severe comorbidity. Our experiences contradict the old – fashioned opinion of performing cranioplasty after 1 year or even more. Off course the costs for 3D implants surmount the costs for other techniques of cranioplasty. However, on the other hand, short operating time, a low complication rate, and consequently a shorter time of hospital treatment, justify our recommendation that taylored implants are the best proposition for the reconstruction of large skull defects today.

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Lessons from National and International TBI Societies and Funds like NBIRTT

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Summary

While Neurotrauma is a growing public health problem worldwide, governments have not been able to respond to the silent epidemic of brain injury. Neurotrauma, according to the World Health Organization, will surpass many diseases as the major cause of death and disability by the year 2020.

Not-for-profit organizations, professional societies and foundations have begun to address the problem of Neurotrauma through educational conferences, training seminars, prevention activities, passage of laws and regulations, and by providing grant funding.

Private sector partnerships with government entities appear to be a significant means of addressing a major public health problem.

Keywords: Traumatic brain injury; neurotrauma; professional societies; foundations; not-for-profit organizations; silent epidemic.

Introduction

Neurotrauma is a significant international public health problem that receives little support and insufficient funding from government and private entities. Many in the public health field call Neurotrauma, the "silent epidemic". Worldwide the incidence of Neurotrauma is on the increase due in large part to the increase in vehicular traffic without proper road infrastructure and traffic controls and by violence, from war and interpersonal violence. According to the World Health Organization injury, especially Neurotrauma, will surpass many common diseases as the most significant cause of death and disability by the year 2020.

This chart illustrates the comparison of traumatic brain injury to other leading injuries or diseases in the United States. The cost of traumatic brain injury in the United States is estimated to be $48.3 billion annually. Hospitalization accounts for $31.7 billion and fatal brain injuries cost the US $16.6 billion each year. Even with these staggering statistics the United States spends less then $50 million annually on research into prevention and cure. Why? Neurotrauma is not a disease or condition that has rallied or gained support from leaders, kings, queens, presidents or celebrities. No one wants to stand up in public and say I have brain damage, when so much emphasis in the global economy is placed on being smart and quick. It is not a cause that has attracted media attention like aids or cancer. So what can be done and what is being done? Just like other conditions and diseases Neurotrauma must begin to use the international press and multimedia to get the word out. Here is where foundations and societies can make a difference. Just think what the late Princess Diana did for awareness of land mines or what Elizabeth Taylor has done for aids, then you can see the possibilities for Neurotrauma. Scientists need to make their research available to the lay public in terms they understand.

Societies and foundations can help with this work and can raise awareness and funding. Let me share with you some examples. In the United States the Brain Injury Association of America of which I am the past president was responsible for passing through the Congress, the first legislation on traumatic brain injury. The TBI ACT sets out standards and provides funding. When I visited the United Kingdom in the early 90's I attended a meeting at Oxford that resulted in the creation of the International Brain Injury Association that has sponsored world congresses in Denmark, Sweden, Italy, Spain, Brazil and in 2005 in Australia. These congresses have raised awareness and produced many changes in the care and treatment of persons with TBI. The Brain Trauma Foundation has produced evidence based guidelines for the management of acute TBI which are used internationally; similarly they have produced evidence based guidelines for the management of penetrating head injury

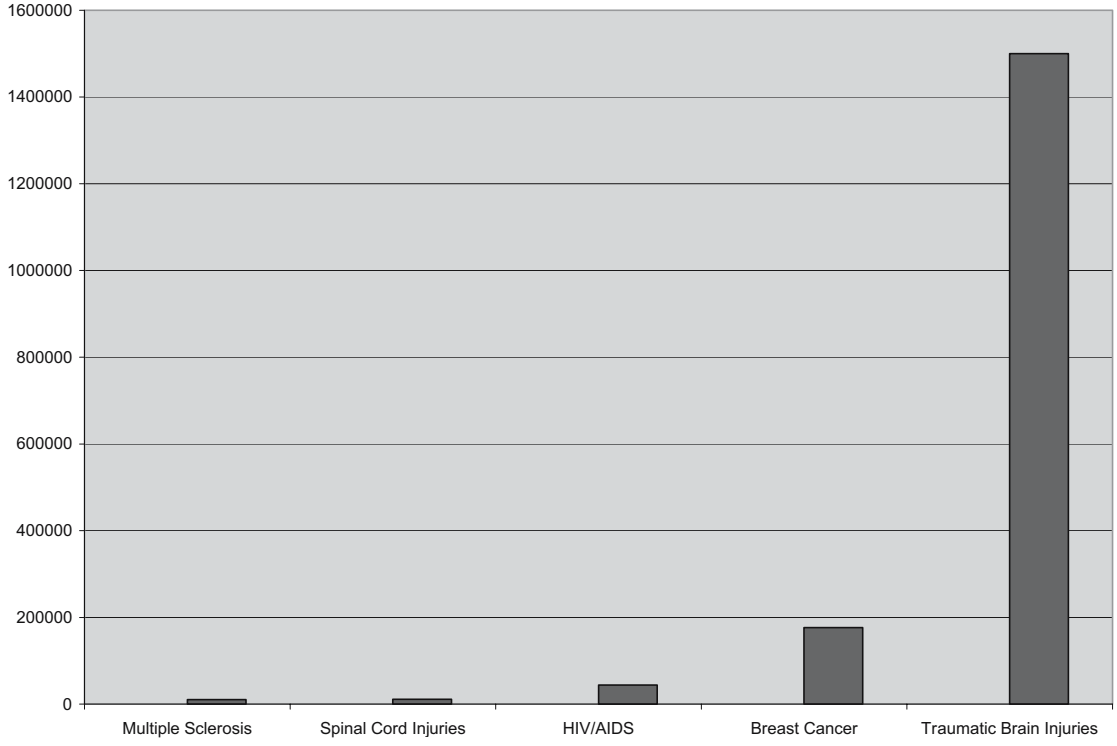

Fig. 1.

which have resulted in approved outcome according to Professor Potapov of the Burdenko Institute in Moscow. Other evidence-based guidelines have been developed in Italy for mild head injury and in other places resulting from the work of societies. Professor Eddie Neugebauer of Germany and Professor Jean-Lux Truelle of France with support from the National Brain Injury Research, Treatment and Training Foundation are developing and international tool to measure quality of life after brain injury. The QOLIBRI is currently being field-tested. It will be very useful in measuring outcomes. When Professor Klaus von Wild founded EMN and AMN he did so to encourage scientific exchange on a European and international basis. Perhaps the most important aspect of private societies and foundations is the role they play in raising funds for research, education, and training.

I will use as example the National Brain Injury Research, Treatment and Training Foundation [NBIRTT] that I established. It has as its purpose the support of cutting edge research, innovative treatment, education and training including the development of evidence based guidelines. NBIRTT has helped to fund the Neurotrauma programs of EMN, the working group on quality of life, evidence based guidelines, the work done to train emergency medical staff and first responders for Neurotrauma, research on new drugs, research on bowel and bladder problems of a neurogenic nature, publications, conferences sponsored by EMN, AMN, IBIA, and special meetings in India, Russia, Brazil, Hungary, the Czech Republic, Austria and WHO Neurotrauma meetings. How is this done, grants are provided based on a review by a scientific panel and based on need.

I believe the impact of these societies and foundations has been profound. There is more sharing of information, technology, research and training. Through increased awareness there are new rehabilitation program springing up across the world, the media is beginning to pay attention and more emphasis is being placed on prevention of Neurotrauma.

In closing I want to tell you about an international meeting that NBIRTT is planning for October of 2005. It will be held at the John P. Murtha Neurosciences Center of the Conemaugh Health System in Johnstown, Pennsylvania. It will be by invitation only. I will invite major neuroscientists, researchers, technology experts, clinicians, pharmacologists and business and

government leaders from across the globe to assemble for three days to establish a consensus document that lays out a five year research agenda to find a ''cure'' for brain damage and its sequelae and to dramatically improve outcomes leading to better quality of life. The goal will be to get agreement and to use this document to establish a $100,000,000 dollar research fund. I hope you will join with me. Please support societies trying to move the field of Neurotrauma forward. Thank you.

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C. Re-engineering of spinal cord lesions

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Brachial plexus surgery (Honorary lecture)

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Summary

Brachial plexus injuries (B.p.i.) are lesions occurring more and more frequently due to high velocity road and sport traumas. They are severe lesions with disabling sequelae. Surgical procedures and results could greatly be improved in the last 2 decades. Although the anatomy of brachial plexus is well known, less known are the functional maps of the various brachial plexus elements.

In this paper treatment modalities for obstetrical, traumatic (adult) and actinic B.p.i. are being described too.

Keywords: Brachial plexus surgery; obstetrical plexus palsy; traumatic plexus injury; neurotisation; nerve grafting.

Introduction

Brachial plexus injuries (B.p.i.) are lesions occurring more and more frequently due to high velocity road and sport traumas. They are severe lesions, often very severe, which will at any rate leave disabling sequelae.

Modern microsurgical treatment of B.p.i. dates back to 1970 (Narakas – Millesi – Brunelli). A great improvement of both surgery and results took place in the last two decades.

The anatomy of brachial plexus is well known, less known are the functional maps of the various elements of brachial plexus which have been drawn by both intra-operative electrical stimulation and dissections. *(Fig. 1 Functional map, Brunelli 1978)*.

It is also important to recognise the functional arrangement of the trunks and cords. *(Fig. 2)*

At the level of the decussation all the axons bound to extension and supination advance in posterior direction whereas all the axons bound to flexion and pronation take an anterior course.

We distinguish obstetrical B.p.i., traumatic (adult) B.p.i. and actinic B.p.i..

– *Obstetrical palsies*: may be distinguished in upper lesions (Duchenne – Erb) and total plexus lesions.

Obstetrical B.p.i. may be due to elongation, rupture or avulsion of the roots from the cord.

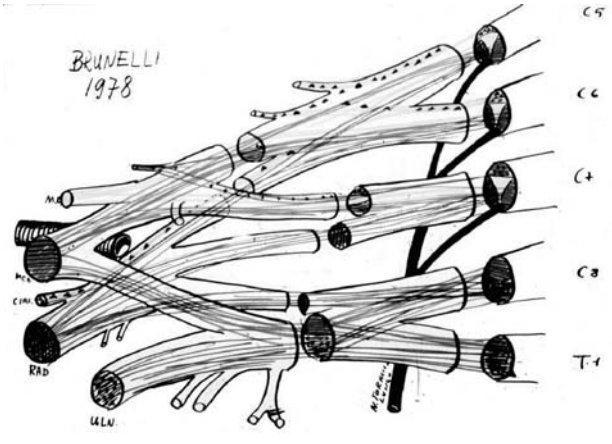

Fig. 1. Functional map of the brachial plexus

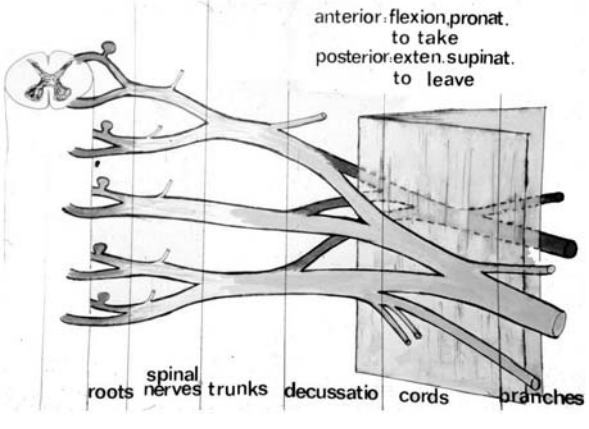

Fig. 2. Functional arrangements of the trunks and cords

In the upper obstetrical B.p.i. (roots C5, C6 or C5, C6, C7) the upper limb is kept in pronation and internal rotation. Active abduction is not possible, the fingers flex actively.

In the total obstetrical B.p.i. the whole upper limb is flail; often the Bernard Horner sign is present.

The natural history of obstetrical B.p.i. includes: a) recovery in a few days if it is a matter of neuroapraxia, b) recovery in months if there is no loss of axon continuity, c) persistence of palsy in case of loss of continuity or root avulsion.

In order to decide whether the palsy has to be treated by surgery we must see if the activity of the biceps muscle starts within the first 3 months. If it does, abstention and continuous observation is advisable, if not, surgery must be done.

Myelography has been abandoned due to both its invasivity and false positive or negative results.

While waiting for surgery, passive mobilisation, massages and exponential electrotherapy should be administered.

Surgery consists of neurolysis, sutures, grafts or neurotisation according to the type of lesion (as it is described in adult B.p.i. surgery – vide infra).

– *Traumatic* (adult) B.p.i. may result from closed or open injuries, stab or gun shots.

Open injuries allow immediate recognition and treatment of the lesion.

Closed injuries may cause: neuroapraxia, axonotmesis (in continuity or not), neurotmesis and avulsion from the cord.

Traumatic B.p.i. may inflict the whole plexus, the upper elements (Duchenne – Erb), the lower elements (Dejerine – Klumpke) or the intermediate elements (C7, Brunelli).

Adult B.p.i. may be located at roots, trunks, cords, terminal and collateral branches.

Vascular injuries may be associated (a. anonima, a. succlavia, a. humeralis) as well as bone fractures (clavicle, scapula and humerus).

Diagnosis is mainly based on physical examination and M.R.I. Myelography has been abandoned due to its invasivity, E.M.G. is often misleading.

A chart of the muscular score (from 0 to 5) is very useful which may be marked in boxes, grouped in different colours and under the roots and trunks, so that at a glance one can make a diagnosis of the damaged elements and locate the level of the lesion (Fig. 3). The sensory palsy, Bernard Horner sign, and vascular lesions are also denoted in the chart. The adjacent boxes serve to mark the score at different spans of time to see the possible improvement.

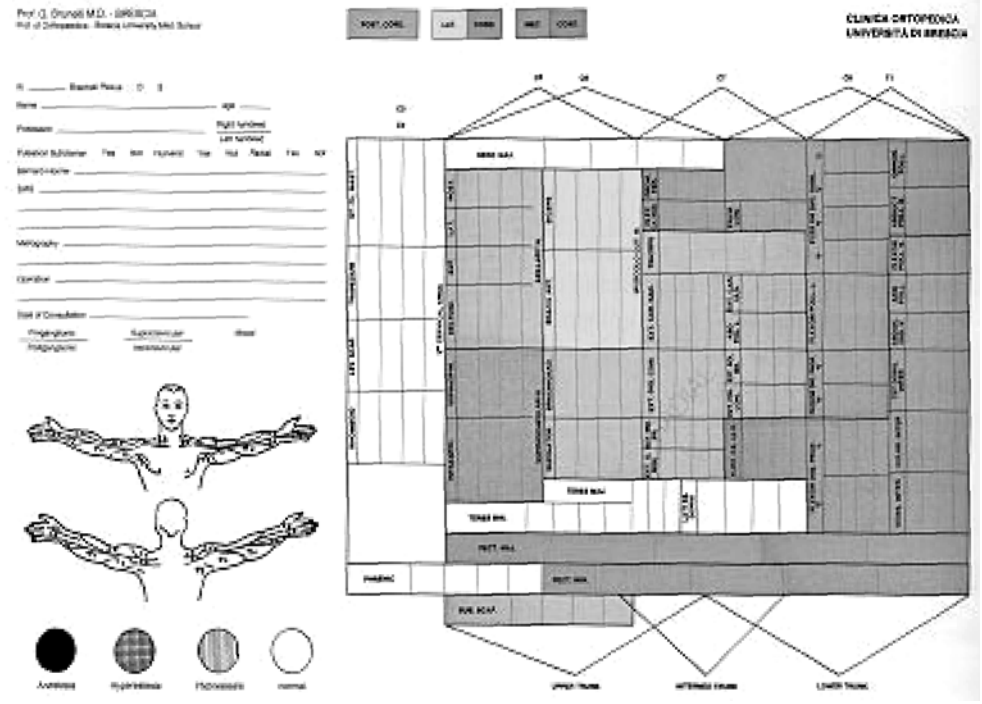

Fig. 3. Muscular score in the brachial plexus injury

The adult B.p.i. may be supra-ganglionic or infra-ganglionic. The supra-ganglionic lesions are more severe and generally consist of avulsion of the roots from the cord with no possibility of suturing or grafting at the level of proximal stump.

Clinically they may be recognised by the sensory-sweating dissociation.

If sensation is lacking and sweating is present, the lesion is located proximal to the sympathetic ganglion. Avulsion of the roots may be seen by contrast M.R.I. which shows either meningoceles or absence of the root appearance.

Timing of surgery: Surgery must be performed as soon as the diagnosis has been made.

It will always be performed at once if total palsy with Bernard Horner sign is present.

Observation is advisable only in closed injuries with negative M.R.I. appearances.

The descending positive or negative Tinel sign and the positive or negative evidence of re-innervation of the more proximal muscles will guide the clinical decision.

While waiting, electrical stimulation of the paralysed muscle is mandatory as well as joint mobilisation especially of the M.P. joint.

Surgery: The approach must be done through multi-angulated skin incision followed by dissection of the sternocleidomastoid muscle, the clavicle and the delto-pectoral crease (Brunelli). Severe keloids which were almost the rule in the past are thus avoided.

After having cut the superficial and deep fascia and the omohyoid muscle the plexus becomes visible.

If it is too much scarred, it is not worthy to try to dissect the whole scarred mass for it will be a time consuming dissection revealing shabby elements. Furthermore, according to modern philosophy of repair, it is much better to connect the proximal stumps with terminal branches in order to avoid dispersion of axons and co-contractions.

In case of root avulsion, a neurotisation has to be performed. Fig. 4 shows root avulsion at various levels. Motor and sensory rootlets are evident, the latter show the sensory ganglion.

Two types of neurotisation are possible: the intra-plexual and the extra-plexual ones.

Intra-plexual neurotisation can be carried out in case of avulsion at one level, in peculiar cases at 2 levels. It consists of distribution in the distal stumps of the avulsed spinal nerve or trunk of part of the fibres of another spinal nerve or trunk whose proximal stump is available.

Fig. 4. Root avulsions at various levels

If more spinal nerves are avulsed, neurotisation is possible by transferring extra-plexual unimpaired nerves to the denervated elements of the injured plexus.

The accessory cranial nerve, the intercostal nerves and the anterior nerves of the cervical plexus are mostly used. In peculiar cases also the phrenic or the hypoglossal nerve may be used.

For extra-plexual neurotisation the donor nerves must be sutured to terminal branches of the plexus in order to avoid dispersion of fibres and harmful co-contractions.

When grafting, it is better to do aimed connections according to the functional maps. It can be performed by single sutures only and not by cable glueing.

Recently avulsed brachial plexus has been operated by transferring the contralateral C7 root (by means of a graft) to the musculocutaneous nerve.

The result is fair. It can animate only one function. Brain adaptation is difficult as C7 carries fibres with very different functions.

I myself have even transferred the whole contralateral ulnar nerve which has branches with well defined functions. Its proximal motor branch is sutured to the musculocutaneous nerve to obtain flexion

of the elbow whereas its two distal branches are led to the nerves of the FCR and ECRL.

Flexion of the elbow is useful to carry a bag but the result is very poor if function of the major pectoral muscle is absent (thoraco-brachial pinch).

If the muscles moving the scapula are spared, a shoulder arthrodesis in 40° of abduction and neutral rotation can restore a useful arm activity, especially if C8, T1 are spared.

The reconstructive surgery (palliative operations) is always to be kept in store to diminish disability. A number of tendon transfers have been used to restore a useful hand according to the spared or recovered muscle.

The flexion of the elbow in partial B.p.i. may be restored by transferring the triceps or the inferior belly of the major pectoral muscle in the distal palsies or by the Steindler operation in the proximal palsies.

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Results in brachial plexus palsy after biceps neuro-muscular neurotization associated with neuro-neural neurotization and teno-muscular transfer

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Summary

None of the currently used techniques for elbow flexion recovery in brachial plexus recovery offers enough strength for normal life activities. The association between several methods grants a better result by a summarizing effect compared to each method used separately. The paper reveals the improvement of the functional results in brachial plexus reconstruction by combining the techniques of nerve repair (nerve grafts, nerve transfers or direct muscular neurotization) with palliative muscular transfers. Of the 54 cases of microsurgical reconstruction of brachial plexus palsy, in 20 cases we associated a muscular transposition: 7 latissimus dorsi transfers (5 monopolar and 2 bipolar), 5 pectoralis major and 8 triceps transfers. The direct neuro-muscular neurotization of the biceps – EMG efficient – was associated with a muscular transfer in 8 cases: in 4 of the 7 latissimus dorsi transfers, in 3 cases of triceps transfer and in 2 case of pectoralis major transfer. The association of the 3 methods – direct neuro-muscular neurotization, neuro-neuronal neurotization and muscular transfer – has a summarizing effect in the flexion restoration of the elbow flexion, which represents a major problem in the brachial plexus palsy.

Keywords: Brachial plexus reconstruction; neuro-neuronal neurotization; neuro-muscular neurotization; muscular transfers.

The treatment for brachial plexus palsy can be frustrating because of the long time elapsed between the moment of the repair and the functional result and the difficulty of solving all problems caused by an extensive lesion [2–4]. The most important decisions to take are what function should be restored first and by which means – nerve repair, neurotization or palliation [15]. The therapeutic strategy has to be adapted to each patient, depending on the type of lesion and all individual characteristics (age, time from the injury, personal needs and preferences). The usual approach is to restore the functions from proximal to distal and for this reason, restoring elbow flexion is one of the prime objectives [6].

There are two main approaches in brachial plexus repair: microsurgical reconstruction or palliative operations using the spared muscles. There are several factors that influence the type of approach, one the most important being the level of the lesion. Nakaras [15] has classified the plexus lesions into 6 zones, but for practical purposes, the classification of Alnot [2] is simpler more easy to use:

Narakas classification (1981) of brachial plexus lesions

1st zone –	between the spine and the conjugation hole – medullar avulsions and radicular ruptures
2nd zone –	between the conjugation hole and the primary trunk that is 3 cm below
3rd zone –	the area of the primary trunks, ranging from 2 to 3.5 cm
4th zone –	secondary trunks, with lengths from 3–5 cm
5th zone –	the distal area of the plexus, comprising the branching of the posterior secondary trunk (circumflex, radial, subscapular and great dorsal nerves) and the "M" of the median nerve
6th zone –	the origin of the nervous trunks, at a few centimeters from the secondary trunks emergence

– supra – and infraganglionic lesions – for the roots
– supra – and retroclavicular lesions – for the trunks

– infraclavicular lesions – for the trunks and terminal branches.

In the case of the 1st level, it is impossible to perform microsurgical reconstruction, while the more distal lesions can be repaired.

The second decisive element is the extent of the lesions and the number of nervous elements affected. The most frequent close lesions of the brachial plexus through traction and elongation are located supraclavicularly and concern the roots C5 and C6 (Erb) and sometimes C7 [15]. Complete paralysis of the brachial plexus or the inferior type C8-T1 are more rare.

The clinical presentation of the Erb paralysis includes the impossibility of abduction and external rotation of the arm and elbow flexion. If the lesion is at root level, paralysis of serratus anterior, rhomboid and levator scapulae can be also present, which contraindicates any attempt to microsurgical repair [2]. The order of priorities in these cases is the recovery of the elbow flexion, followed by the re-establishment of arm abduction and eventually by ensuring the sensitivity on the median margin of the forearm and the hand. If the results of the microsurgical reconstruction of the neural elements are insufficient for a useful function, the arc of mobility and strength can be improved with muscle transfers [1, 7]. In this regard, the muscles available for elbow flexion are the latissimus dorsi, the pectoralis major, the triceps brachialis and more rarely used the pronator-flexor mass [17].

Material and methods

Between 1995 to 2002, 54 patients with traumatic lesions of the brachial plexus aged from 19 to 56 were treated. 38 of them were male and 16 female (%).

The time elapsed from the accident ranged from 8 to 27 months, with an average of 14 months.

In most cases (52 out of 54), the traumatisms were closed, by elongation or traction; only in 2 cases the plexus lesions were produced by wounds at a supraclavicular level.

In 45 cases the microsurgical reconstruction of the brachial plexus was performed by grafts or neurotization, in 11 cases of which muscular transfers were associated and in the rest of 9 cases only palliative interventions took place.

The performed palliative muscular transfers used the latissimus dorsi in 7 cases, the triceps brachialis in 8 cases and the pectoralis major in 5 cases. The evaluation of the functional results made at an interval of 6–22 months, with an average of 14 months. The followed parameters were active and passive mobility, muscular force and functional utility of the affected limb in daily activities.

The *latissimus dorsi* transfer was the first option if its innervation was unaffected and its force was fully preserved. In 5 cases we used a muscular flap, while in the remaining 3 the flap was musculocutaneous. In 4 cases the transfer was unipolar (Fig. 1) and in 4 cases bipolar by proximal reinsertion at the level of the coracoid apophysis.

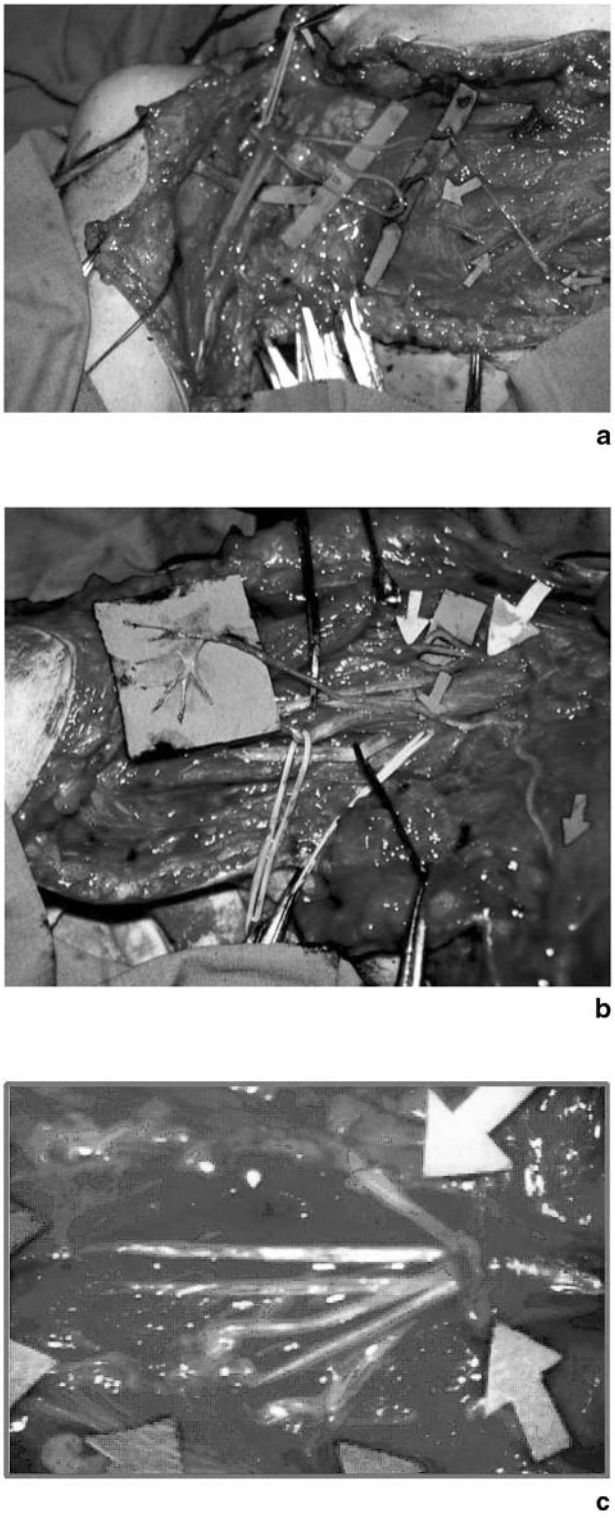

Fig. 1

There were no complications and all flaps survived completely. No unipolar transfer determined any compression on the branches of the brachial plexus.

After more than 6 months, we could evaluate 5 patients. The

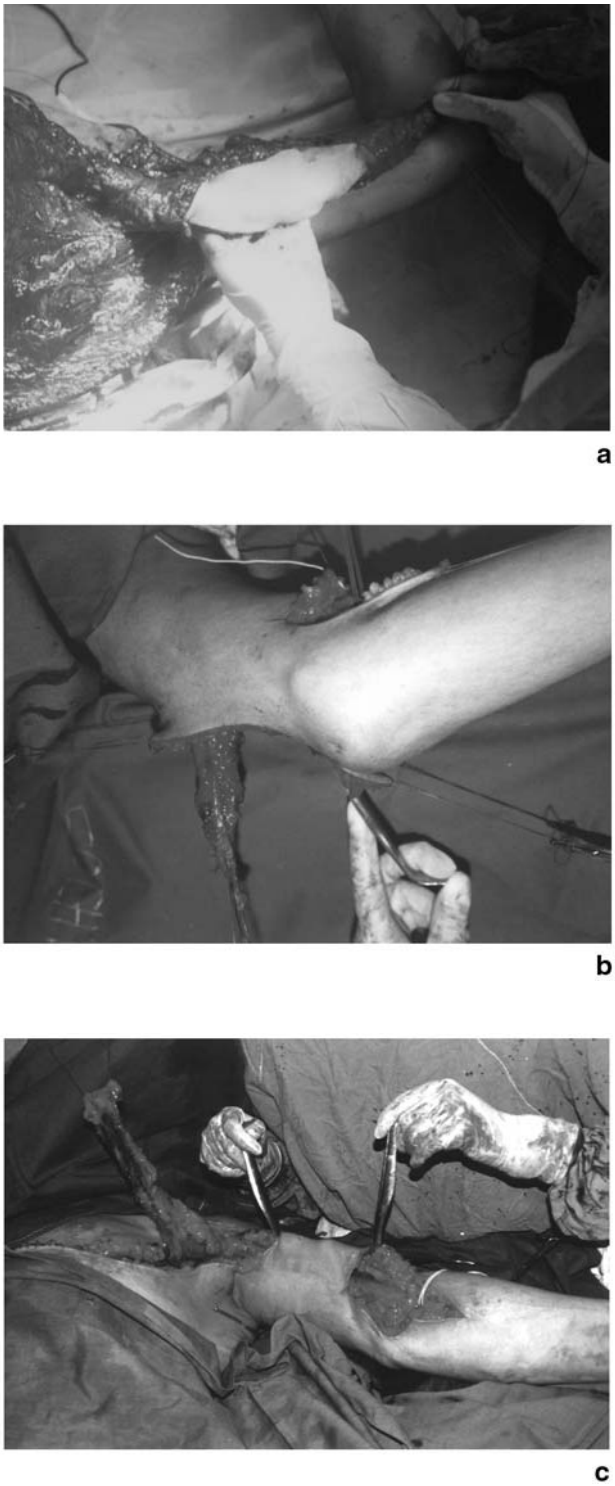

Fig. 2

active mobility arch ranged from the lowest value of 85° (between 15° and 100°) to the highest value of 110° (between 5° and 115°). Muscular force ranged from 5 to 11 kg, with an average of 8 kg.

For the *anterior transposition of the triceps tendon*, we preferred

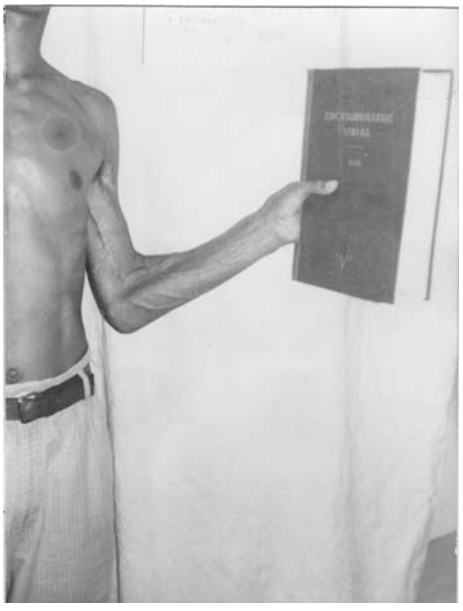

Fig. 3

the Carroll technique, of suturing the triceps on the bicipital tendon (Fig. 2) rather than the original Bunnell technique that requires the reinsertion on the radius by means of a tendinous graft. Besides the easiest surgical technique, the Carroll operation has the advantage of keeping the effect of antebrachial supination of the biceps, an important aspect due to the paresis that is often associated with the supinator muscle.

The maximal active flexion obtained in the 3 cases we could review was of 90°, 95° and 105° and the gravitational passive extension had a deficiency of 5 to 15°. The force of the elbow flexion was of 2, 3.5 and respectively 4.5 kg. We should mention nevertheless the fact that we obtained the poorest results with female patients, generally with a lower muscular force.

In the 4 cases using the *pectoralis major*, we applied the Clark technique of unipolar muscular transfer (Fig. 3). All the flaps were muscular and passed at the level of the arm by subcutaneous tunneling. All flaps were designed as distal as possible up to the level of the rectus abdominis so after rotation, we could suture it directly to the bicipital tendon.

The follow up of 4 cases for more than 6 months after the operation revealed a maximal degree of flexion of 110–115° in all cases, with an extension deficiency of no more than 10°. The muscular force ranged from 4.5 to 7 kg.

In all cases the immobilization after the operation was performed with the elbow flexed at about 110° for 4 weeks after which the functional reeducation began. In the first 3 weeks from the start of mobilization, the elbow extension was limited to 60° with a dorsal splint.

Discussions

The choice of the reconstructive method in the palsies of the brachial plexus depends first on a most correct evaluation of all motor deficits on the one hand and of the still functional muscular groups on the other

hand. This diagnosis should be clinical and electromyographic and completed if needed with imaging explorations like RMN and myelography in order to establish the level of the lesion and so the indication for microsurgical reconstruction.

The most frequent being the superior palsies (Erb), the degree of impairment of the musculature in the vicinity of the shoulder – pectoralis major, latissimus dorsi and triceps brachialis – should be attentively evaluated, because any force or contractility deficit may alter the therapeutic benefit [18].

Microsurgical reconstruction of the brachial plexus should be attempted in all young patients seen within the first 6–8 months after the accident [20].

In brachial plexus reconstruction there are two ways of neurotization that can be combined: 1) neuro-neuronal – nerve grafts or nerve transfers [13] – and 2) direct muscular neurotization [8]. Direct muscular neurotization is based on four phenomena [7]: a) axonal growth stimulation by neurotrophic factors, b) increased sensibility of the denervated muscle for the motor axons, c) new motor plates formation in the aneural zone of the muscle and d) the "adoption" phenomenon by which each motor axon reinnervates 2–3 muscular fibers leading to giant neuro-muscular plates formation (GNMP). By the way of GNMP, the direct muscular neurotization can reinnervate up to 50% of the muscular fibers. Nerve reconstruction alone by grafts or nerve transfers allows reinnervation of 50–70% of muscular fibers at the level of the original end-plates. The reinnervated muscular fiber by direct muscular or neuro-neuronal neurotization does not accept additional innervation in either way. The sequence: direct muscular neurotization followed by neuro-neuronal neurotization ensures a more rapid reinnervation from the direct neurotization, while the slow growing axons from the neuro-neuronal neurotization through a longer distance will later reinnervate an additional percentage of the remaining denervated muscular fibers, improving the functional outcome. On the electromyogramm (EMG), the reinnervation potentials of the direct muscular neurotization are later enriched by those due to neuro-neuronal neurotization. Motor unit potentials (MUP) have a variable aspect and a high amplitude with a late component. The polyphasic potentials are gradually replaced by MUP in parallel with stabilization of the reinnervation process.

If the result is not satisfying, muscular transfers can further enhance the functional outcome. Palliative surgical interventions by muscular transfers are indicated in the following circumstances [11]:

- plexal lesions are too proximal (Narakas zones 1 and 2) in order to be able to be repaired microsurgically
- failure or insufficient result of nervous repair
- too much time elapsed since the accident, with the installation of an irreversible amyotrophy
- when associated surgical techniques – microsurgical nerve reconstruction and palliative interventions – are planned from the beginning.

In all cases when the innervation of the latissimus dorsi was not impaired, its transposition is to be preferred because of the very good functional results and the recovery of a higher flexion force compared to the other interventions and the sequels of the donor area are functionally minimal and esthetically acceptable [5, 9, 14]. Yet, if the muscle was paretic at a first stage after which it recovered its contractility, we should rather choose another muscular transfer because most often it does not regain sufficient force for a useful elbow flexion [10, 12].

In the cases mentioned above, the best alternative is the pectoralis major. We always preferred the Clark technique of unipolar transfer, leaving in place its sternal portion, in order not to destabilize the shoulder in patients who did not have an arthrodesis. The force and the range of elbow flexion are sufficient for all current activities, yet the esthetic sequels contra-indicate it in the case of women [18].

For the patients who don't need a great force, but prefer a simpler surgical intervention, the anterior transposition of the triceps is the preferable intervention, because the produced functional deficiency is acceptable for persons with a lower physical activity and who do not usually work with hands above their shoulders or push objects [19].

We should rather use the Carroll operation than the Steindler palliative, because we think that it is preferable to have an active extension deficiency of the elbow rather than face the risks of finger retraction when flexed or forearm retraction in pronation, which would impair more the functioning of a limb already affected.

In conclusion, the association of the 3 methods – direct neuro-muscular neurotization, neuro-neuronal neurotization and muscular transfers – have a summarizing effect in the flexion restoration of the elbow flexion, offering the perspective of a maximal functional result.

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Macrophages and dendritic cells treatment of spinal cord injury: from the bench to the clinic

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Summary

The failure of the spinal cord to recover after injury has been associated with the immune privilege mechanism that suppresses immune activity throughout the central nervous system. Primed macrophages and dendritic cells were shown to promote neurological recovery in preclinical models of spinal cord injury. A cell therapy consisting of autologous incubated macrophages is now being tested on spinal cord injury patients in clinical trials.

Keywords: Cell therapy; immune privilege; neuroprotection; neurodegeneration; neuroimmunology.

Introduction

Most tissues of the human body are able to regenerate and repair damage caused by injury or disease. This includes the tissues of the peripheral nervous system (PNS). In marked contrast, the central nervous system (CNS) has virtually no regenerative capacity. Moreover, the initial damage is amplified by the spread of a damage beyond the primary lesion causing extensive functional loss. Thus, a damage to the CNS causes permanent disability, in the case of spinal cord injury (SCI) paraplegia or tetraplegia.

A common strategy in the development of therapeutic options for treating SCI has been to seek to interrupt stages in the damage process. Some of the damage processes targeted are: glutamate toxicity, reactive oxygen and nitrogen species, trophic factor deprivation, growth inhibitors, ion imbalance, etc. None of these approaches have yet led to an effective pharmacological therapy for SCI [6], although since the early 1990's, there has been widespread use of the anti-inflammatory drug methylprednisolone administered in the first hours following SCI, a marginally effective [4, 5, 26] but controversial treatment [10, 20, 22].

In our search for an alternative therapeutic strategy for SCI, our research has concentrated on finding the physiological difference between the CNS and other tissues that may account for their different regenerative capacities. The underlying assumption is that inducing an appropriate physiological response to injury in the CNS may lead to sustained, comprehensive wound healing that overcomes some of the neurological loss. One major difference found is in the activity of the immune system in the different tissues. In most tissues, the immune system is continuously active in countering foreign agents and in removing tissue debris. Immediately after injury, the innate immune response is activated, with blood-borne macrophages arriving at the lesion site where they begin to clear debris and toxic elements. The macrophages also activate the lymphocytes, creating an inflammatory environment that is conducive to tissue renewal. In contrast, immune activity in the CNS is suppressed by a mechanism known as immune privilege, with the resident immune cells (microglia) suppressed by the environment and the entry of blood-borne macrophages almost non-existent after injury. Furthermore, the microglia respond to the injury in a way that may exacerbate the damage. Thus, after injury the CNS environment remains hostile and unsupportive of tissue repair. With increasing recognition of the central role of the immune system in physiological tissue repair [9], the idea arose of developing therapeutic technologies based on introducing elements of the immune system into the injured CNS.

Rationale for using macrophages and dendritic cells for treatment of spinal cord injury

In most non-CNS tissues, macrophages are primary players in the immune response to injury, being the first cells to arrive at the lesion site. Here they remove toxic elements and debris, and release cytokines that induce the recruitment of lymphocytes. Additionally, the macrophages act as antigen presenting cells (APCs), presenting debris-derived antigens on the cell surface to cause the specific activation of matching lymphocytes. The activated macrophages and lymphocytes then secrete more cytokines and growth factors that support tissue survival and regrowth. Interferon-γ plays a central role in the process, being the main cytokine secreted by a T-cell after its activation by a matching antigen presented on the APC MHC-II cell surface complex. Interferon-γ then acts on macrophages and similar cells to stimulate their APC activity, thus providing an amplification mechanism.

Though similar to blood-borne macrophages in some respects, CNS-resident microglia are poor APCs. Experiments have shown that microglial cells are responsive to molecules in their environment and the effect of activated microglia can be either protective or destructive depending on the activator used. Microglia activated with molecules such as lipopolysaccharide, amyloid-β and zymosan, known activators of macrophages via the "classical pathway", cause increased cell death in the hippocampus of brain slices (unpublished results). In contrast, microglial cells, activated with Interferon-γ, a major secretory cytokine of activated helper T cells, promote hippocampal cell survival. The two contrasting types of microglial activation are also seen in the resulting metabolic activities of the microglia, with lipopolysaccharide-activation causing enhanced release of nitric oxide but no effect on glutamate uptake, while activation with Interferon-γ has no effect on nitric oxide release but enhances the uptake of glutamate.

Interferon-γ would not normally be expected in the injured CNS, because even though lymphocytes arrive at the lesion site, there are no effective APCs present to activate them, since blood-borne macrophages are excluded and the resident microglia show insufficient APC activity. We suggest that the lack of APCs can be overcome either by supplementing the injured CNS with exogenous APCs, or by vaccination with a CNS-specific antigen to boost the population of suitable lymphocytes.

It has been established that macrophages take on APC-like characteristics after incubation with regenerative tissue such as peripheral nerve tissue or skin [3]. After incubation, the macrophages have elevated MHC-II and co-stimulating molecules (CD80, CD86 and ICAM-1), all molecules participating in antigen presentation. The macrophages secrete pro-inflammatory cytokines, notably Interleukins 1β and 6, but reduced amounts of tumor necrosis factor α. The macrophages also produce growth factors such as brain-derived neurotrophic factor.

Dendritic cells, a type of professional APC, can be produced by culturing bone-marrow cells with interleukin-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF). These cells express very high levels of MHC-II and costimulatory molecules [8].

Effects of macrophages and dendritic cells in animal models of axonal injury

Axonal transection

Optic nerve and spinal cord transection models were used to test macrophages that had been incubated *ex vivo* in environments typical of the injured PNS (co-incubation with sciatic nerve segments) or the injured CNS (co-incubation with optic nerve segments).

When injected into the transected optic nerve, PNS co-incubated macrophages were found to promote myelin clearance [11], considered a prerequisite for axon regeneration [24]. Treatment with the PNS co-incubated macrophages was also found to restore axon continuity [12]. In contrast, macrophages that had been co-incubated with CNS-tissue proved to be ineffective.

In experiments conducted using the rat spinal cord transection model, injection of PNS co-incubated macrophages to the severed spinal cord resulted in partial reversal of paraplegia, with meaningful motor recovery observed in 15 of 22 macrophage-treated animals, while none of the 47 control rats showed recovery [23]. Neurological recovery after spinal cord transection has also been achieved using skin co-incubated macrophages.

Spinal cord contusion

The rat contusion model is the most thoroughly investigated and frequently used model for SCI and was

found to correlate with human SCI with respect to functional, electrophysiological and morphological outcomes [17]. Contusion is induced using the NYU Impactor [7] to deliver a controlled, reproducible impact to the spinal cord. The intensity of the impact is adjustable, with severe impact resulting in complete neurological loss similar to complete spinal cord injury in humans. The NYU Impactor is currently used in many different laboratories for spinal cord experiments in animals [2, 18, 19, 27].

The time window for macrophage therapy after spinal cord injury was explored using the rat spinal cord contusion model. The following time windows were examined, each representing a different physiological stage:

- Three to four days post SCI-This period reflects the decline of primary infiltration of neutrophils participating in inflammation, and high incidence of apoptotic cells [14, 15, 21, 25];
- At 7–10 days post SCI there is maximum proliferation and/or accumulation of ED1-positive cells (activated microglia/macrophages), T-cells, and progenitor glial cells [14–16];
- At 14 days post SCI the numbers of ED1 positive cells and T cells are still very high. At the same time different cytokines and chemokines in the injured tissue decrease or disappear [13–16];
- 21 days post SCI many of the injury-induced biochemical and cellular activities in the spinal cord have peaked and begun to return to normal levels [13, 14, 16].

Rats were implanted at different days post contusion with skin co-incubated macrophages that had been purified from contused donor rats and co-incubated with skin as described above. The results presented in Fig. 1 indicate a beneficial effect on motor recovery 8–9 days after injury, a time at which T-cell accumulation reaches a peak.

It has also been found that several months after contusion, the spinal cords of macrophage-treated rats have significantly less cysts [3], suggesting that therapy with incubated macrophages has the potential to reduce the extent of Syringomyelia.

Administration of dendritic cells also results in improved motor recovery and reduced cyst formation in spinally-contused rats [8]. The effect was obtained with dendritic cells that had been preloaded with native myelin basic protein (MBP) or an altered peptide derivative. However, unloaded dendritic cells or cells preloaded with a foreign antigen (ovalbumin) showed no beneficial effect. Moreover, the beneficial effect of MBP-loaded dendritic cells was not obtained in T-cell deficient (thymectomized) spinally-contused rats.

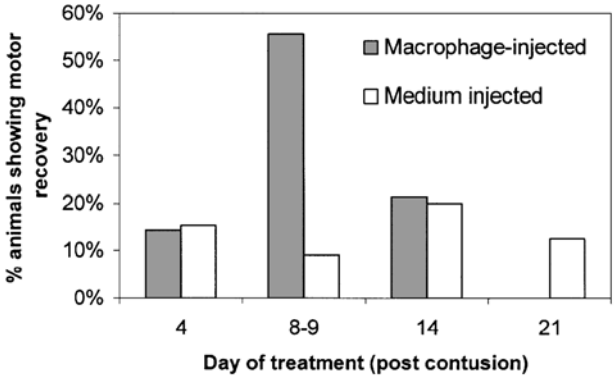

Fig. 1. Time window for treatment of spinally contused rats with skin co-incubated macrophages. Rat macrophages were prepared from donor rats that were contused at spinal segment T8 on the same day as the recipient rats. The macrophages were isolated on the day before implantation and then incubated with rat skin tissue according to a standard protocol [3]. The recipient rats received approximately 1.5×10^5 macrophages (ED1-positive cells) suspended in 5 μL medium, injected into the spinal cord immediately caudal to the lesion site. Control rats were injected with medium only. Meaningful recovery was based on the percentage of animals in the group achieving a motor score of at least 6 using the open-field locomotor assessment scale [1]

Application for treatment of human spinal cord injury

The data summarized above demonstrate the beneficial effects of macrophage and dendritic cell therapy in several rat models of axonal injury, including a spinal contusion model that resembles typical human SCI. Following extensive preclinical safety studies, an autologous incubated macrophage therapy is now being developed for treatment of acute SCI in humans. It is hoped that the new therapy will improve neurological function and reduce the extent of syringomyelia. Phase 1 clinical trials have been completed on 14 patients with complete SCI, who all received autologous skin co-incubated macrophage implants within two weeks of injury. No significant therapy-related adverse events have been observed during follow-up of up to 3 years. Five of the patients have shown an improvement in neurological grade (as defined according to the American Spinal Injury Association impairment scale), and their injuries are no-longer defined as complete. A Phase II clinical trial is now underway.

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Electrophysiological effects of 4-aminopyridine on fictive locomotor activity of the rat spinal cord in vitro

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Summary

Recently the K^+ channel blocker 4-aminopyridine (4-AP) has been suggested to be useful to improve motor deficits due to spinal cord lesions. There is, however, little basic research support for this action of 4-AP. In this study we have used as a model the neonatal mammalian spinal cord in vitro that generates a rhythmic activity termed fictive locomotion (induced by bath-application of NMDA + 5-HT) with phasic electrical discharges alternating between flexor and extensor motor pools and between left and right motoneurons within the same segment. When 4-AP was added in the presence of sub-threshold concentrations of NMDA + 5-HT, there was facilitation of fictive locomotion which appeared with alternating patterns on all recorded ventral roots (VR). Furthermore, in the presence of 4-AP, weak dorsal root (DR) stimuli, previously insufficient to activate locomotor patterns, generated alternating discharges from various VRs. The present data show that 4-AP could strongly facilitate the locomotor program initiated by neurochemicals or electrical stimuli, indicating that the spinal locomotor network is a very sensitive target for the action of 4-AP.

Keywords: Central pattern generator; spinal cord lesion; rhythmic patterns; oscillations.

Introduction

Fampridine-SR, a new sustained release oral tablet form of 4-AP is currently under phase III clinic trial for its therapeutic efficacy in patients with Multiple Sclerosis (MS) and chronic spinal cord injury [2]. The rationale for this approach stems from the fact that low concentrations of 4-AP are considered to block transient, voltage activated, outward K^+ currents. The most striking effect seen with K^+ channel blockers is an enhancement of transmitter release at many central and peripheral synapses as a consequence of increased Ca^{++} influx into presynaptic terminals.

4-AP sensitive K^+ channels are also present in the internodal area of the axon membrane shielded under the myelin sheath. Traumatic injury causes apoptosis of oligodendrocytes with disruption of the myelin wrapping which then unmasks 4-AP sensitive K^+ channels located in juxtaparanodal and internodal regions. The activity of such previously-hidden K^+ channels results in axonal conduction failure at central and peripheral level [5]. Hence, block of voltage-dependent fast K^+ channels by 4-AP has two important effects that are thought to ameliorate the central conduction deficit experienced by patients following MS or traumatic cord injury: it prolongs the duration of the action current in focally demyelinated internodes and it enhances central and peripheral synaptic transmission.

We have considered the possibility that 4-AP might improve spinal cord function by modulating and/or reactivating the operation of the specialized spinal network devoted to generate rhythmic motor patterns responsible for locomotion. Such network is named Central Pattern Generator (CPG). The spinal CPG can generate in vivo, even in the absence of external stimuli, phasic electrical discharges alternating between flexor and extensor motor pools and between left and right motoneurons within the same segment.

A very similar pattern can be produced also by superfusing the isolated mammalian spinal cord with excitatory agents like NMDA and serotonin (5HT; see [1, 3]) or by repeated stimuli applied to one DR [4]. Since the main rhythmic burst in L2 is flexor-related and the main burst in L5 is extensor-related, it is common to call the rhythmic activity locomotor-like when the L2 and L5 bursts alternate on one side of the cord and when there is segmental left-right alternation.

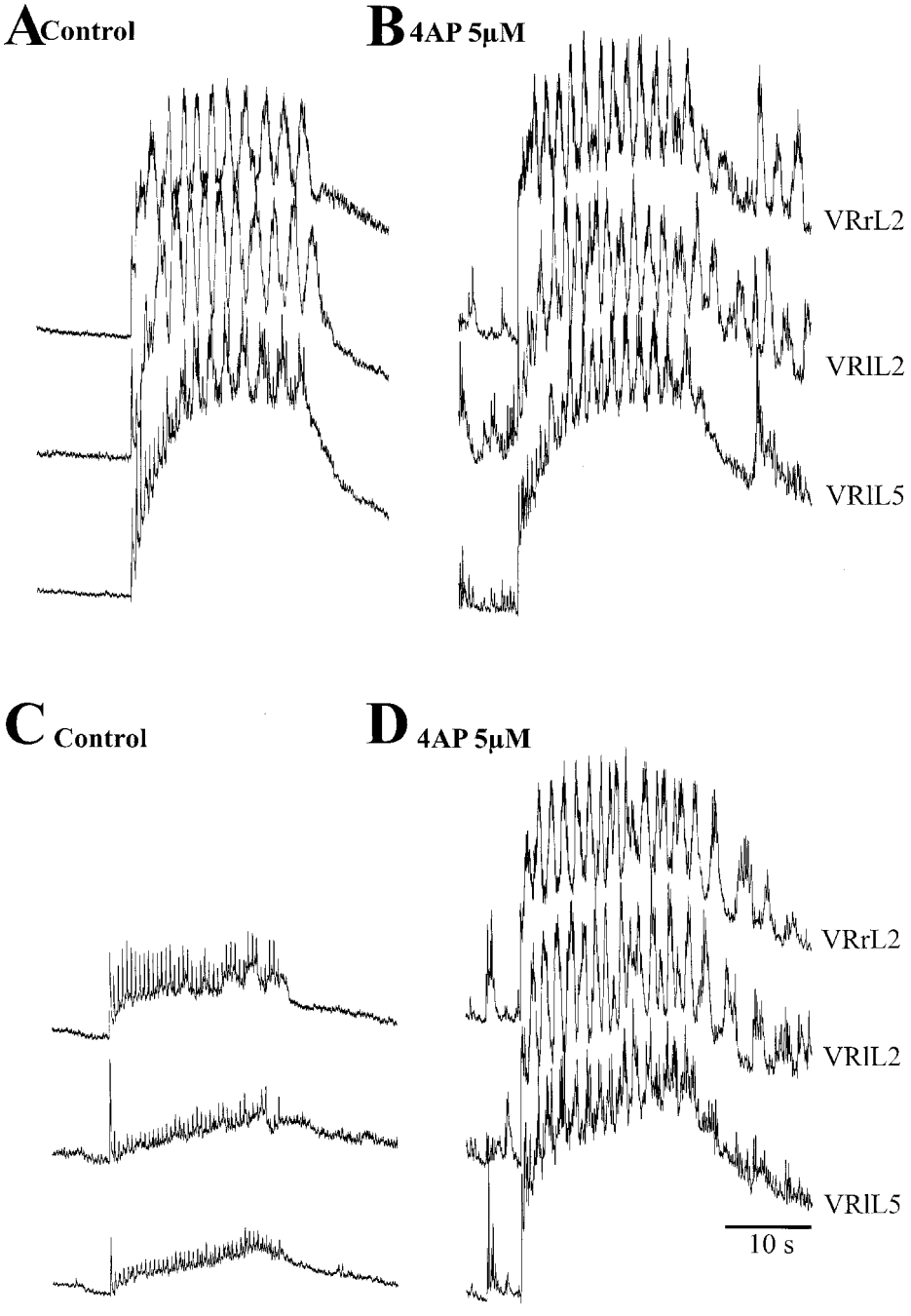

Fig. 1. 4-AP enhances alternating motor patterns during DR stimulation. Sample records are from three VRs (left, l, and right, r) whose segmental identification is abbreviated alongside the traces. All data are from the same preparation. (A) During a train of 40 strong pulses to a single DR, there is a slowly developing VR depolarization with superimposed alternating patterns. (B) When the test is repeated in the presence of 4-AP the number of alternating patterns is clearly increased. (C) The same preparation is stimulated with a train of weak DR pulses unable to induce cumulative depolarization or oscillations. (D) When the test is carried out in the presence of 4-AP, there is appearance of cumulative depolarization and alternating oscillations

Because of its well defined inputs via DR fibres and motor output via VR axons, and because of its long-term stability, the isolated spinal cord of the rat represents a very advantageous in vitro model to evaluate the pharmacological action of drugs, like 4-AP, proposed for the symptomatic treatment of spinal cord injured subjects. The present study sought to clarify if 4-AP could act on the spinal CPG.

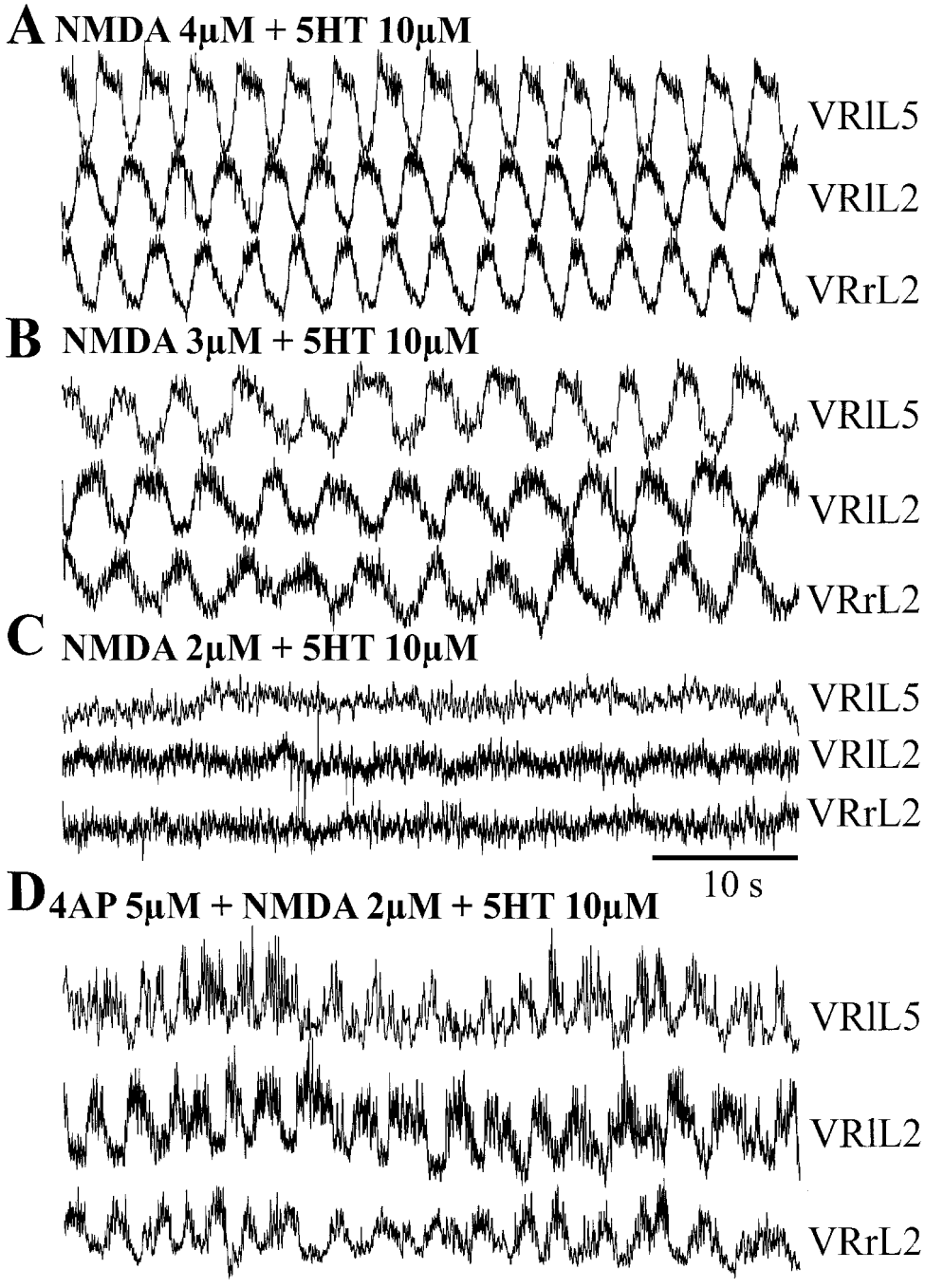

Fig. 2. Fictive locomotion is disclosed by 4-AP. Representative traces are all from the same preparation. (A) Stable fictive locomotion is recorded in the presence of 4 μM NMDA and 10 μM 5-HT. Note alternation between flexor and extensor motor pools. (B) Decreasing the NMDA concentration to 3 μM slows down the rhythm. (C) When the NMDA concentration is 2 μM, the rhythm is suppressed. (D) Administration of 5 μM 4-AP restores the rhythm despite the low concentration of NMDA

Methods

In accordance with NIH guidelines and the Italian act DL 27/1/92 n. 116 (implementing the European Community directives n. 86/609 and 93/88), experiments were performed on lumbar spinal cord preparations isolated from neonatal Wistar rats (0–5 days old) under urethane anaesthesia (0.2 ml i.p. of a 10% w/v solution). The experimental set-up was the same as described by Taccola *et al.* (2004) [6]. In brief, the neonatal rat spinal cord was superfused (7.5 ml min^{-1}) with Krebs solution of the following composition (in mM): NaCl, 113; KCl, 4.5; $MgCl_2 7H_2O$, 1; $CaCl_2$, 2; NaH_2PO_4, 1; $NaHCO_3$, 25; glucose, 11; gassed with 95% O_2–5% CO_2; pH 7.4 at room tempera-

ture. All agents were bath-applied via the superfusing solution at the concentrations mentioned in the text. In view of the need to record fictive locomotion rhythms for a long time, the majority of experiments were based on DC-coupled recordings from lumbar VRs. DR electrical stimuli were employed to elicit either single VR responses (recorded from the ipsilateral VR of the same segment) or VR cumulative depolarization following a train of DR pulses.

Fictive locomotion was typically induced by continuously bath-applied NMDA plus 5-HT.

Results

A low concentration (5 μM) of 4-AP could not trigger the expression of fictive locomotion as this drug generated synchronous oscillations only (not shown). We therefore explored if 4-AP could facilitate the genesis of fictive locomotion in the presence of appropriate stimuli to the spinal locomotor CPG. Figure 1 A–B shows extracellularly recorded cumulative depolarization of three lumbar VRs following a train of 40 strong electrical pulses to a single DR. The cumulative depolarization which developed gradually during the pulse train presented superimposed alternating oscillations. In control condition such oscillations occurred between lL2 and lL5 and between rL2 and lL2, thus featuring the hallmarks of fictive locomotion. 4-AP (5 μM) increased the cumulative depolarization area by enhancing the number of oscillations without affecting their period. Note that during cumulative depolarization the synchronous oscillations induced by 4-AP disappeared to be replaced by the alternating ones.

The same experimental procedure was repeated by using a train of much weaker electrical pulses (see Fig. 1 C–D), which in control condition could evoke neither cumulative depolarization nor alternating oscillations. When this test was repeated in the presence of 4-AP (5 μM), the same stimulation pattern could now generate cumulative depolarization with alternating oscillations.

Figure 2 A shows a representative experiment of stable fictive locomotion induced by application of NMDA (4 μM) and 5HT (10 μM). This rhythm shows the characteristic double alternation between right and left side of the cord and between flexor and extensor motor pools. A small decrease in NMDA concentrations to 3 μM decelerated the rhythm which preserved its alternating patterns (Fig. 2 B). When NMDA was applied at 2 μM (Fig. 2 C), the rhythm disappeared. However, application of 5 μM 4-AP (in the presence of subthreshold concentration of NMDA and 5HT) could readily restored fictive locomotion (Fig. 2 D). When 4-AP was applied during a stable fictive locomotor pattern, it accelerated the rhythm (not shown).

Discussion

The present data show that 4-AP could strongly facilitate the locomotor program initiated by neurochemicals or electrical stimuli indicating that the operation of the central pattern generator responsible for locomotion could be significantly up-regulated by a very low dose of 4-AP. The present data therefore indicate a novel site of action for 4-AP in facilitating spinal motor programs in addition to its effects on axons and peripheral synapses. This effect of 4-AP was strictly dependent on the coincidence of 4-AP administration and stimulatory inputs to the CPG. For this reason 4-AP may have a possible therapeutic application to bring the CPG activity to threshold, although by itself it could not generate fictive locomotion.

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Alternative, complementary, energy-based medicine for spinal cord injury

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Summary

This paper provides an overview on various alternative, complementary, or energy-based therapies that expand the healing spectrum of individuals with spinal cord injury (SCI). Not only do they have the capability to help a variety of secondary conditions, they have the ability in some people, for certain injuries, to restore function, sometimes dramatically. After providing an overall contextual rationale for the use of alternative medicine, this paper briefly summarizes various Eastern-medicine healing modalities, laser-based therapies, nutritional and homeopathic approaches, and pulsed electromagnetic therapies.

Keywords: Spinal cord injury; alternative medicine; complementary medicine.

Introduction

Definition

Definitions of alternative medicine vary greatly. For example, in the West, acupuncture is an alternative therapy, but in China, it is traditional medicine. Dr. D. Eskinazi (New York, NY) defines it "as a broad set of health-care practices (i.e., already available to the public) that are not readily integrated into the dominant health-care model because they pose challenges to diverse societal beliefs and practices (cultural, economic, scientific, medical and educational) [7]."

Trends

Eisenberg *et al.* (Boston, MA) reported that 40% of Americans used alternative therapies in 1997; and between 1990 and 1997, visits to alternative practitioners jumped 47% and Americans visited alternative providers 629 million times compared to 386 million visits to primary-care physicians [6]. Sixty-four percent of US medical schools offer some courses on alternative medicine; in Europe, 40% of medical schools and 72% health-sciences faculties provide such training [2]. Analyses of the 1999 US National Health Interview Study indicate individuals with disabilities use alternative medicine even more than able-bodied individuals [9].

Concern about side effects

Although modern medicine's many contributions have greatly benefited people with SCI, it also has a down side that inordinately affects them. Examples include: 1) 106,000 people die from adverse drug reactions annually in US hospitals, making it the nation's fourth to sixth leading cause of death [16]; 2) 2,000,000 people who enter hospitals in the US get infections that they did not have when they went there. Of these, 80,000 die [8]; 3) according to the National Academy of Sciences, medical mistakes kill 44,000 to 98,000 people annually [15]. These statistics are especially relevant to people with SCI, who are often prone to overmedication, life-threatening infections, and more hospitalization; and warrant a consideration of alternatives.

Double blind or double standard

Although many alternative therapies are not supported by rigorously designed scientific studies, the Congressional Office of Technology Assessment and others have concluded that only 10–20% of medical interventions physicians practice are scientifically proven [1]. Most conventional, as well as alternative, medicine is not based on carefully designed clinical trials but on a history of use and experience.

Cost

Most of the World's population cannot afford high-technology Western medicine. For example, Somalia's

per-capita healthcare cost is $11 compared to over $5,000 in the US. Because of such economic healthcare disparities, the World Health Organization has recommended that alternative, complementary, and indigenous medicine be integrated into national healthcare policies and programs [26].

Eastern based therapies

Acupuncture

Traditional Chinese Medicine believes that a life-force energy called qi permeates all living things through channels called meridians. Under traditional theory, traumatic paraplegia is the consequence of damages in the Du or Governor meridian. Acupuncture's goal is to clear and activate meridian channels, reversing qi stagnation.

At a NIH Consensus Development Conference, Dr. M. Naeser (Boston, MA) summarized studies that treated CNS paralysis with acupuncture [17]. One study reported that 95% of treated individuals with SCI had some improvement, such as improved sensation, bowel and bladder function, spasms, and walking [27]. Other studies suggest that electroacupuncture may be beneficial in the treatment of neurogenic bladder [4] and syringomyelia [25].

Scalp acupuncture is a specialized form of acupuncture that has helped many people with nervous-system disorders, including SCI [13]. Although treatment is usually initiated long after the acute injury phase, the most optimal therapeutic window, most patients have accrued significant quality-of-life-enhancing health benefits.

Qigong

With disability, qi can stagnate and become unbalanced, increasing the likelihood of illness. Hence, it is important to stimulate qi flow, using, for example, qigong, a healing exercise that encompasses gentle movement, breathing, and meditative practices. With slight adjustments, it is possible to practice most of these practices from standing, seated or, even lying down positions, and, with or without arm movement.

Many with SCD have accrued significant benefit from qigong-related practices. Dr. R. Trieschmann (Phoenix, AZ) used qigong-related practices to improve the overall health and functioning of people with physical disabilities. For example, through these practices, an incomplete quadriplegic was able reduce his devastating central cord pain; and a woman legally blind due to multiple sclerosis was able to improve her sight enough to drive and read [24]. Trieschmann states: ''Both of these individuals were massively depressed by their circumstances and had lost all hope that life could be better for them. Yet by understanding the role of energy in their life and changing the methods of managing their energy, they have been able to produce change in their function at the physical level even though a myriad of physicians could offer no hope for any improvement in their condition.''

Ayurveda

India's ancient healing tradition focuses on wellness and disease prevention. Paralysis results in considerable physiological and metabolic shifts, which from an Ayurvedic perspective, increase the divergence between one's current mix of doshic energies and one's born-with doshic-energy ideal. If this imbalance is not corrected, health will be compromised. Hence, those with paralysis need to be especially vigilant in their efforts to retain a good doshic balance through diet and life style.

In rats with peripheral nerve injury, regeneration was 30–40% higher in animals treated with the Ayurvedic herb Mimosa pudica [19]. The results of a limited self-report, pilot study carried out by the author in paralyzed veterans noted a variety of subtle effects in subjects with spinal cord dysfunction.

Laser-based therapies

Growing evidence indicates that laser-based therapies have considerable potential to treat SCI-associated problems:

Laser-acupuncture hand therapy

Dr. M. Naeser has developed an effective alternative therapy for carpal tunnel syndrome (CTS), which affects many manual wheelchair users, and spasticity-related hand-flexion problems [18]. This therapy specifically stimulates hand acupuncture points with a low-energy laser beam and a mild electrical current generated from a TENS device. Rigorously designed clinical studies indicate 90% of treated individuals will have significant, enduring relief from CTS pain.

Functional recovery

Dr. S. Rochkind (Israel) has carried out extensive research using laser therapy to treat peripheral nerve and spinal cord injuries. In one study, of 31 patients with severe spinal cord cauda equine injuries that were treated with laser therapy, half showed some degree of functional motor improvement [21].

Another Rochkind study examined effects of embryonic cell transplantation and laser therapy on recovery after SCI in rats. Results indicated that the most effective re-establishment of limb function and gait performance, transport of electrophysiological signals, and histological parameters occurred after cell implantation and laser irradiation, compared to transection alone or implantation without laser treatment [11].

Finally, Byrnes *et al.* (Bethesda, MD) demonstrated that laser energy alters gene expression in rats after acute SCI [3].

Nutrition

Many nutritional approaches enhance the wellness of individuals with SCI, including:

Creatine

Miami Project investigators demonstrated that creatine supplementation increases exercise and respiratory capability in individuals with complete cervical SCI [10]. After supplementation, improvements were noted in various respiratory measurements, including oxygen uptake, CO2 production, tidal volume, and breathing rate.

Urinary tract infections

Studies suggest that drinking cranberry juice greatly reduces bacterial attachment to cells lining the bladder in subjects with SCI [20]. Studies also suggest that D-mannose, a naturally occurring sugar that binds to bacterial cell-surface lectins, is even more effective than cranberries in dislodging E. coli bacteria from the bladder wall [12].

Homeopathy

Homeopathy can help individuals with SCI enhance their overall wellness, reduce heavy medication burden, and preserve life-saving antibiotic effectiveness. In randomized double-blind clinical trials, Dr. E. Chapman (Boston, MA) has shown that homeopathy significantly lessens the symptoms and improves functioning in mild chronic head injury [5], suggesting the possibility that effects may be also be observed for SCI.

Pulsed electromagenetic fields

Many studies suggest that pulsed electromagnetic fields (PEMF) exert beneficial effects for a variety of neurological disorders:

First, Dr. W. Young (New York, NY) showed that Diapulse-generated PEMF (Diapulse Corp., Great Neck, NY) reduces calcium at the injury site in cats, preserving function. Specifically, the majority of Diapulse-treated cats were walking four months after surgery compared to none in the control group and that the device was superior to treatment with the now post-injury treatment standard methylprednisolone [28]. Second, Weiss *et al.* (Poland) treated 97 acutely injured patients with Diapulse, of whom, 38 had pronounced neurological improvement, including 28 with substantial functional gains and 18 being discharged with only slight extremity impairment [14]. Third, Dr. M. Sambasivan (India) showed that Diapulse therapy reduces cerebral edema and mortality after head injury [23]. Finally, Salzberg *et al.* (Valhalla, NY) demonstrated that Diapulse-treated SCI-related pressure sores healed on average in 13 compared to 31.5 days for controls [22].

Conclusion

This talk summarized a few of the many alternative, complementary, energy-based healing modalities that expand the healing armamentarium for individuals with SCI. There is a world of opportunity beyond the banks of the mainstream.

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The effect of penile vibratory stimulation on male fertility potential, spasticity and neurogenic detrusor overactivity in spinal cord lesioned individuals

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Summary

Purpose. Present the possibility for treatment of male infertility, spasticity, and neurogenic detrusor overactivity in spinal cord lesioned (SCL) individuals with penile vibratory stimulation (PVS).

Method. Obtaining reflex-ejaculation by PVS, by using a vibrator developed for this purpose. The stimulation was performed with a vibrating disc of hard plastic placed against the frenulum of the penis (amplitude $\geq$ 2.5 mm). The vibration continued until antegrade ejaculation or for a maximum of 3 minutes followed by a pause of 1 minute before the cycle was repeated, maximally 4 times.

Results. >80% SCL men are able to obtain ejaculation with PVS. Pregnancy rates obtained with home PVS and intra-vaginal insemination was 22–62% (4 studies), and with PVS or electro-ejaculation and intrauterine insemination/in-vitro fertilization/intracytoplasmatic sperm injection 39–64% (9 studies). PVS was demonstrated to decrease spasticity significantly when measured by the modified Ashworth scale. In addition, a decrease of the number of spontaneous EMG events which probably indicate spasms was observed. Increase in bladder capacity at leakpoint following 4 weeks of frequent ejaculation with PVS treatment was likewise demonstrated.

Conclusion. PVS has proved its importance for SCL male fertility, in the years to come its place in treatment of spasticity and neurogenic detrusor overactivity has to be established.

Keywords: Spinal cord injury; penile vibratory stimulation; spasticity; neurogenic detrusor overactivity; male fertility.

Introduction

Spinal cord lesioned (SCL) individuals suffer from a number of disabilities, of which some of the most common are sexual dysfunction, urinary bladder problems, and spasticity and spasms in the lower extremities [11]. How severe these challenges are depends on the level and completeness of the spinal cord lesion.

Penile vibratory stimulation (PVS) has been used for more than 20 years [4] as a method to obtain ejaculation in SCL men with the purpose of fertilisation. Since the early 1990ies the method has been the standard treatment for SCL men with a wish of fertilisation at Rigshospitalet, Copenhagen University Hospital, Denmark.

Over the years clinical observations have shown a reduction in lower extremity spasticity and spasms following reflex ejaculation induced by PVS. In addition there have been indications that ejaculation induced by PVS might increase bladder capacity.

The aim of this presentation is to give a brief overview of the possibility of using PVS in alleviating some of the severe consequences of SCL and at the same time avoid some of the potential side-effects inherent with treatments of today, e.g. spasmolytics, anticholinergics, and irreversible surgery.

Penile vibratory stimulation

PVS to induce ejaculation was first described in 1965 in non-SCL men. The first reported use of PVS in a SCL man was in 1970 [2], but Brindley [4] has been largely responsible for popularising the use of PVS in men with SCL.

It seems that during PVS a "normal" ejaculatory reflex is induced. Successful ejaculation by PVS in SCL men seems to require an intact spinal cord at the level of T_{10}-S_4 in order to have an intact ejaculatory reflex arc to allow transmission of afferent stimuli to the sacral spinal cord (S_{2-4}), communication between the sacral and thoracolumbar regions (T_{10}-L_2), and efferents from both of these spinal cord regions.

Antegrade ejaculation is seen only in men with complete cord lesions above T_{10}, but no other absolute predictors of the ejaculatory response are identified related to reflexes, completeness of lesion, somatic reactions, age or time since SCL [19]. However, when the reflexes and/or somatic reactions such as erections, abdominal muscle contractions and leg spasms are present during PVS there is observed a higher frequency of men with antegrade ejaculation.

The PVS procedure is performed with the SCL man placed in the supine or sitting position. The PVS activate the ejaculatory reflex via the afferent penile dorsal nerve by application of a vibrating disc of hard plastic against the frenulum penis for a period of up to 3 minutes until antegrade ejaculation occurs. If no ejaculation has occurred the stimulation period is followed by a rest period of 1–2 minutes and stimulation begins again. The required time to induce ejaculation by PVS ranges from 10 seconds to 45 minutes [2].

Already Brindley [4] noted that the output of the vibrators and, in particular, the amplitude might have some effect on the ejaculatory response. Several non-medical vibrators have been used and the vibratory output has been poorly standardized. The highest rates of ejaculation (antegrade plus retrograde) have been seen with a vibrator amplitude level of ≥ 2.5 mm. The ejaculatory responses were similar irrespective of whether the investigator, the SCL man or his partner performed the procedure [19].

For the purpose of inducing reflex ejaculation in SCL men, both in the clinic and at home a special user-friendly vibrator has been developed (Ferti Care® *personal*, Multicept A/S, Gørløse, Denmark). Adjustments of the vibrator have made it possible for many tetraplegics to use it by themselves despite poor hand function.

All procedures of assisted ejaculation, including PVS, in SCL men with lesions above T_6 may provoke an acute episode of autonomic dysreflexia. This condition is usually experienced by a sudden pounding headache due to increase in the blood pressure. Flushing, sweating, and cardiac arrhytmias are other common symptoms. To prevent autonomic dysreflexia nifedipine is given sublingually 10 to 15 minutes prior to PVS in men with SCL above T_6. During the first procedures the blood pressure should be monitored until the right dose of nifedipine has been established. In general, significant complications from PVS are rare. Local skin abrasion is a common finding but no treatment is necessary other than a short rest period [2].

Male fertility potential and PVS

The ability to procreate naturally is lost in the majority of SCL males due to ejaculatory dysfunction and abnormal semen characteristics. The reported ability to ejaculate during sexual stimulation or masturbation range from 0 to 55% (median 15%) [18]. The characteristics of semen obtained from men with SCL are below normal levels, in particular, the sperm motility rates.

The rates of ejaculation (antegrade plus retrograde) obtained with PVS, with a vibrator amplitude of 2.5 mm and a frequency of 100 Hz have been 83–96% [19].

The unique advantage of PVS is the possibility of home use. PVS and vaginal self-insemination performed by the couple at home is a viable option for those SCL men with adequate semen parameters. The SCL man and the partner should be carefully instructed at the hospital in the PVS procedure. SCL men with a lesion at or above T_6 should be instructed to self-administer nifedipine prophylactically to prevent autonomic dysreflexia, if they are prone to this syndrome. If the autonomic dysreflexia is not well controlled they are not candidates for home PVS. A non-spermicidal container is used for collection of the ejaculate and a 10 ml syringe is used for vaginal self-insemination.

It is reported, that multiple ovulation cycles were used to achieve the home pregnancies and the overall pregnancy rate per couple is 25–61%. The ovulation timing is important, while the use of luteinising hormone detection kits should be evaluated to determine if these improve the home pregnancy rates [2].

The PVS will in addition allow the majority of SCL couples to perform the procedure themselves at the hospital when a specimen is required in connection with assisted reproduction techniques. Several successful pregnancies have been reported [2, 20] using spermatozoa obtained by PVS or electroejaculation combined with assisted reproduction techniques such as intrauterine insemination or in-vitro fertilisation with or without intracytoplasmatic sperm injection. The overall pregnancy rate per cycle from those studies is about 25%, and this rate is similar to the pregnancy rate per cycle during natural procreation in healthy couples wanting to become pregnant although assisted ejaculation procedures and reproduction techniques are required for SCL men and their partners [2].

Several fertility treatment options are available to

enhance the reproduction prospects in SCL men and their partners. The proper choice of treatment should be made through coordinated efforts of different specialities, which may involve urology, gynaecology, andrology and rehabilitation. It is also of importance to inform the couples about possible side-effects from hormonal ovulation induction as well as challenges related to multiple births.

Spasticity/spasm treatment with PVS

In previous studies a reduction in lower extremity spasms and, in particular, spasticity has been reported in SCL individuals following reflex ejaculation induced by PVS [19, 21]. In addition Halstead *et al.* [7] observed relief of spasticity in SCL men as well as women using rectal probe electrostimulation, which usually is used for ejaculation in men.

In a very recent study [13] including nine SCL men with self-reported spasticity and/or leg spasms PVS was tested. Their age ranged from 27 to 67 years, the time since spinal cord lesion from 4 months to 50 years, and their levels of lesion were C2 to T8. Six had motor complete and three motor incomplete lesions.

24 hours electromyography (EMG) measurements were carried out using surface-electrodes at the quadriceps femoris and tibialis anterior muscles bilaterally to measure the frequency of spasms in the lower extremities. In analysing the EMG recordings the chosen criterion for a spasm was EMG with activity exceeding 4 times the baseline and with duration longer than 5s, called an ''event''. Modified Ashworth Scale (MAS) [3] was used for clinical assessment of spasticity in the legs using a total evaluation of the muscle tone in the flexors and extensors of the knees and ankles, and the Penn Spasm Frequency Scale [16] was used for subjective evaluation of the frequency of spasms in the legs.

All participants were allocated randomly into two study groups. In both groups 24 hours of EMG recording from the lower extremities were performed initially followed by either a session of PVS or ''no treatment''. Subsequently, a new period of 24 hours EMG recording was performed. After at least one week, those men who had PVS, now received ''no treatment'' and those men who had ''no treatment'' previously now received PVS and again they had 24 hours of EMG recording before and after. MAS was performed at study entry, 24 hours after PVS or ''no treatment'', and again after 48 hours. The SCL men gave their subjective evaluation of the effect of the treatment by grading the spasm-frequency with the Penn Spasm Frequency Scale during the 24 hours before PVS or ''no treatment'' and then again 24 hours after this.

The SCL men were all asked to maintain their daily life with their usual level of physical activity. Also, they were told to write a dairy with all incidents differing from their usual activities such as extraordinary physical activity and hours at rest. Their medication was kept constant during the study period.

A statistically significant reduction in the number of EMG events during the first three hours after PVS (mean = 10.07) was found when comparing to the number of EMG events in the three hours prior to vibration (mean = 17.58) ($p < 0.05$). The largest reduction occurred in the first hour after PVS after which it gradually decreased until no significant effect was observed in the third hour after vibration. A similar reduction was not observed following ''no vibration''. The clinical evaluation revealed a significant decrease in muscle tone after PVS as evaluated by MAS ($p < 0.01$). When the subjects were clinically evaluated again 24 hours later this reduction in muscle tone had vanished. The subjects spontaneously reported that they experienced a relaxation in the legs and a reduction in the spasm frequency following vibration and there was a trend towards a decrease in the number of spasms according to the Penn Spasm Frequency Scale, but this did not reach a statistically significant level ($p = 0.26$).

In five of the males antegrade ejaculation did not occur by PVS and no investigations were made to confirm if retrograde ejaculation had occurred. Whether it is necessary to stimulate until the point of antegrade ejaculation is unknown, but the results suggest that a more distinct effect is obtained when that point is reached.

Neurogenic detrusor overactivity treated with PVS

A significant increase in bladder capacity due to suppression of urinary detrusor reflex activity has previously been observed in one SCL man following PVS induced ejaculation [14].

In a later study [15] 14 SCL men with urodynamically documented neurogenic detrusor overactivity participated. There were no specific criteria concerning bladder capacity or detrusor pressure. Their age ranged from 24 to 62 years. Time since SCL was from

1.5 to 24 years, and their levels of lesion C4 to T7. Twelve had motor complete and two motor incomplete lesions. Five used suprapubic tapping and nine intermittent catheterisation for bladder emptying.

All the SCL men had tried PVS before and achieved ejaculation with the procedure. They were instructed not to use PVS for at least two weeks before entering the study in order to minimize any possible pre-effect of PVS on urinary bladder function. All participants had a baseline cystometry done. Two days later a second cystometry was performed immediately after PVS ejaculation in order to examine the acute effect of PVS ejaculation on the urinary bladder. A third cystometry was conducted after one month of ejaculation by PVS every third day at home in order to examine any long-term effects. At the final visit, one to three days later, PVS ejaculation was immediately followed by a fourth cystometry in order to examine if it was possible to achieve any further acute effect in addition to a potential long-term effect.

No statistically significant change in bladder capacity was registered at leak point (V_{leak}) at baseline compared to immediately after ejaculation by PVS. However, V_{leak} increased significantly from a median of 190 mL (17–700 mL) at baseline to 293 mL (30–700 mL) after 4 weeks of frequent PVS ejaculation ($p = 0.03$). No further significant acute effect in V_{leak} was seen.

No significant relationships were found between age, time since lesion, level of the lesion, urinary bladder management, the number of urinary tract infections per year, use of anticholinergic medication, or use of prophylactic nifedipine and V_{leak}. As in the spasticity study [13], the most marked effect on bladder capacity and detrusor pressure was seen in the tetraplegic men with complete lesions.

Clitoral vibratory stimulation in female spinal cord lesioned individuals

When the studies on spasticity and neurogenic detrusor overactivity [13, 15] were designed, they were planned to include the same number of female and male SCL persons, since the mechanism of the treatment was supposed to be the same for both genders.

Technically, the vibratory stimulation in women is carried out with the vibrating disc placed directly on the clitoris.

During recruitment of SCL volunteers, it appeared to be very difficult to make SCL women participate in the studies. Only two women participated and finished the spasticity study [13], and another two SCL women were included in the bladder study [15], but dropped out during the investigation period. The individual results did show the same trends as in the men.

Because of the low compliance of the SCL women, a debate meeting was arranged. The general attitude towards vibration on the clitoris among the SCL women was, that it was not an acceptable method to use as a treatment of physical problems in spite the fact that it could be an alternative to drugs with potential side effects. The SCL women expressed, that vibration on the clitoris would involve both psychological and sexual trauma and feelings, and without the offer of therapy to take care of this, they did not feel comfortable with this kind of projects. These statements should be considered in planning of studies with SCL women [12].

Discussion

PVS has in daily clinical practice for several years in many spinal cord units around the world shown its importance for the improvement of SCL male fertility. In the coming years its possible place in treatment of spasticity and neurogenic detrusor overactivity in SCL men has to be established. Likewise it would be interesting to find out if clitoral vibration may have a place for treatment of spasticity and neurogenic detrusor overactivity among SCL women in the future. There certainly seems to be challenges, which have to be overcome before we will gain the necessary experience within this particular field.

PVS is a method of neuromodulation. Electrical peripheral nerve stimulation is another form for neuromodulation, which likewise has been used in the later years both for treatment of spasticity and neurogenic detrusor overactivity with some success.

Electrical stimulation of the dorsal penile/clitoral nerve has thus been performed in order to inhibit neurogenic detrusor overactivity [6, 10, 17]. In one of the studies [17] in SCL persons, it was not possible to demonstrate the efficacy of the stimulation of the dorsal penile nerve in inhibiting neurogenic detrusor overactivity. On the other hand in two more recently published studies [6, 10] including SCL individuals this stimulation significantly increased cystometric capacity and decreased the detrusor pressure respectively. This electrical stimulation of the dorsal penile/clitoral nerve may be the one most similar to PVS since the stimulus goes through the pudendal nerve to the S_{2-4}

of the spinal cord and from there efferents go to the bladder. But the electrical stimulation is a more direct way of stimulating the nerves, whereas vibration is a transcutaneous, mechanical indirect nerve stimulation, possible through pacinian corpuscles, and then through unknown neural pathways it may induce a "natural" ejaculation reflex. Another major difference is, that peripheral electrical nerve stimulation does not induce ejaculation, and it may be that the ejaculation itself is important for the effects observed after PVS, but this remains to be verified in particular taking the pilot studies in women into consideration, and that several of the male participants in the spasticity study [13] did not obtain antegrade ejaculation during the PVS procedure. Here it is also noteworthy that more distant transcutaneous electrical stimulation of the posterior tibial nerve has resulted in significant decrease of neurogenic detrusor overactivity [1].

Likewise for spasticity various techniques of electrical stimulation have been shown to be effective in the treatment. This includes stimulation to the antagonist muscle to achieve reciprocal inhibition, or tetanic stimulation to the spastic muscle [5]. Further functional electrical stimulation, e.g. of the peroneal nerve, which primarily was used for its effect as a functional drop foot orthosis, has shown to decrease spasticity in SCL individuals [8]. Recently magnetic stimulation applied to the lumbar nerve roots also has been able to decrease spastic tone significantly up to 24 hours [9].

As can be seen several different kinds of neruomodulation seems to be possible both in relation to neurogenic overactive detrusor and spasticity.

The underlying mechanism of the effects of PVS on both spasticity and neurogenic detrusor overactivity remains unknown, and further studies are warranted to elucidate the mechanism behind the effects experienced with the use of genital vibratory stimulation.

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Posttraumatic syringomyelia – a serious complication in tetra- and paraplegic patients

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Summary

Post-traumatic syringomyelia (PTS) is relatively rare, but its complications can be serious.

In the beginning of the operative treatment (1900–1930), scarring could be reduced to a certain degree. In modern treatment (1980–1990) a shunt implantation showed also little effect in long-term follow-up studies. Influenced by the work of B. Williams, 58 PTS patients underwent surgery to create a pseudomeningomyelocele, an artificial CSF reservoir, performed to normalize the CSF flow. In a 10-year-postoperative follow-up study (minimum observation two years), good results were obtained in more than 70%.

Keywords: Spinal cord lesion; paraplegia; post-traumatic syringomyelia.

Introduction

The first description of a posttraumatic syringomyelia (PTS) was given by Bastian in 1916 [3]. The PTS requires a traumatic lesion of the spinal cord and its surroundings, especially if there is a disturbance of the cerebrospinal fluid. Neurological deficits are not necessary [4]. PTS can occur after some years post injury. Bake *et al.* reported that about 51% of patients with spinal cord lesions have cystic spinal cord degenerations, detected in modern imaging e.g. MRI. Symptomatic PTS with growing cavities is found in 2–5% of all patients with spinal cord lesions [6]. Klekamp *et al.* found out that 36% of patients with cervical trauma develop a PTS (53% thoracic and 11% conus medullaris lesions). Progressive neurological symptoms typically occur after a time period of several years. Patients in our series showed an increase in neurological deficit between some weeks and more than 20 years [11]. Barnett (4 and 5) and different other authors have described PTS in incomplete as well as in complete spinal cord injury (SCI).

The theory of aetiology of PTS rests on the disturbance of the spinal pathways and the blockade of the cerebrospinal fluid as Williams [12] showed by some studies. However the exact pathomechanism is yet unknown.

Materials and methods

Between 1989 and 1992 ten of our patients with symptomatic PTS were treated with subarachnoidal shunts. Eight of these shunts had to be changed twice, four of them three times. Based on these problems we consulted B. Williams (Midland Centre Birmingham/UK) and he told us: "It is easy to obtain good results in the short term." . . . "any surgeon can put a drain in a syrinx!" As we learned from our results that occlusion of the shunt may occur in more than 50% of the surgical procedures.

Changing our policy we directed our attention to the cavity itself. Our aim was to prevent refilling of the cavity and to normalize the CSF flow so as to reduce the pulsation of the spinal cord. For that reason we created a so-called "pseudomeningomyelocele" described by Williams in 1992 [12].

Our operative procedure was to perform a laminectomy over two segments localized at the widest extension of the syrinx, usually located close to the spinal cord lesion. The dura was opened widely by longitudinal incision and fixed on the lateral side by stay sutures. The next important step was to free arachnoid adhesions and to ensure CSF circulation from cranial and caudal directions. Bleeding into the cyst had to be minimised to avoid new adhesions. Under microscopic view the myelon was carefully opened laterally by laser or scalpel (intermedial sulcus) to reach the syrinx. A shunt is not needed. To avoid CSF leakage, the dura opening was covered with an artificial dura patch. A median stitch was performed to prevent dura collapse.

Results

During the last ten years (1993–2002), 58 patients were treated with progressive PTS. All of them underwent the procedure described. Thirty four improved

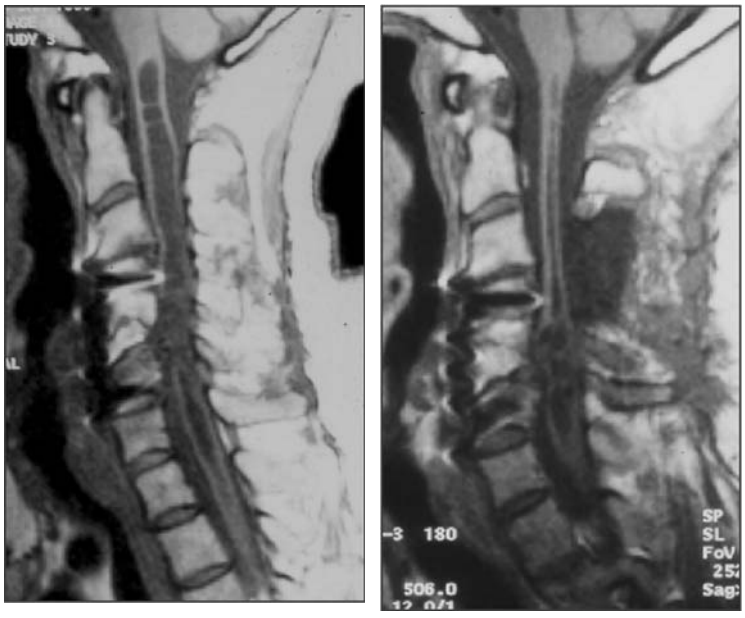

Fig. 1. (a) 8 years post trauma, (b) 2 years post operative

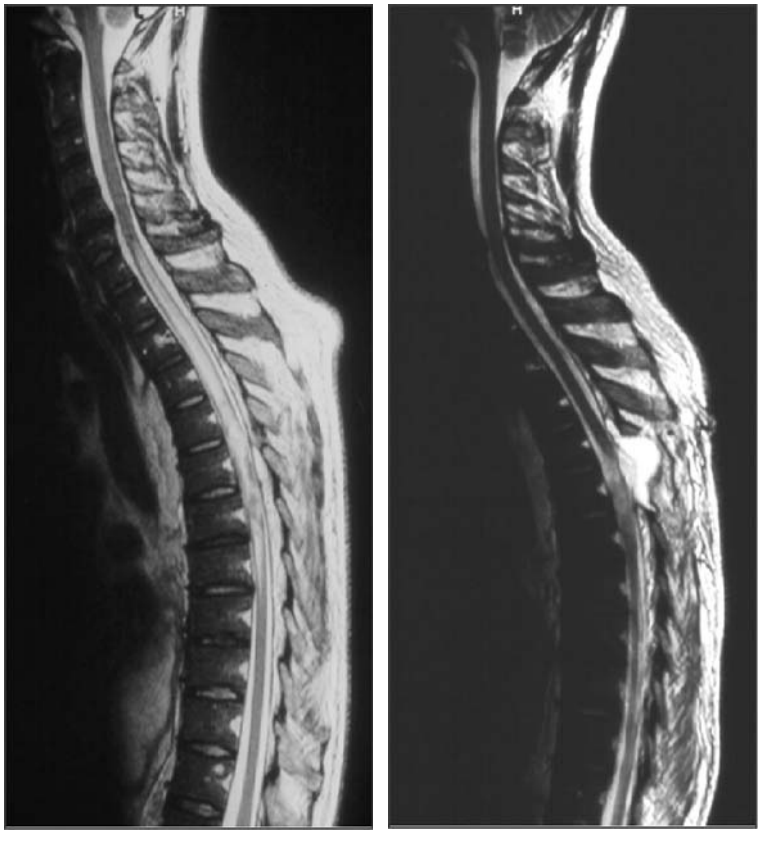

Fig. 2. (a) 15 years post trauma, (b) 4 years post operative

after the operation, 17 remained in a neurologically stable status. Five patients became worse, especially with regard to their pain syndromes. One Patient died from pulmonary embolism.

To sum up, about 70% of the treated patients were in a stable or improved neurological status two years postoperatively.

Discussion

Surgical treatment of a syrinx was first published by Abbe and Coley in 1892 [1]. They punctured the syrinx without neurological improvement. Victor Horsely [7] was the first to treat a syrinx from arachnoiditis by dissecting the scars.

However there are few reports about transection of the myelon leaving the dura open.

Early reports as well as the latest publications favour normalisation of the CSF flow as main target of PTS treatment. Shunting a syrinx was the favourite treatment in the last decade of the past century (see above).

Instability and or kyphotic angulation may force a development of PTS after trauma. Surgical stabilisation of spinal cord injured patients is a treatment method accepted worldwide, but the cord lesion may also be accompanied by arachnoid pathology.

So far there is no clear knowledge of the pathomechanism of PTS which commences in the traumatised spinal cord. However, surgical procedure can normalise the structures surrounding the spinal cord and may help to reduce the occurrence of symptomatic PTS.

The treatment of patients with PTS may lead to a progressive neurological deficit which can be avoided and alleviated if timely MRI investigations are carried out.

Conclusion

In order to reduce neurological deficit in patients with PTS, it is beneficial to obtain normal CSF flow by performing a pseudomeningomyelocele and thus reduce the different power mechanisms onto the spinal cord.

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Functional neurorehabilitation in locked-in syndrome following C0–C1 decompression

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Summary

Today, thanks to intensive care treatment and modern diagnostic tools, increasingly more patients with severe brain and spinal cord lesions, mainly secondary to accidents, stroke, tumours, and congenital malformations survive the acute impact on the central nervous system (CNS). Complicated operative procedures and concomitant complication may also lead to severe impairment of the sensory motor and cognitive behavioural functioning as it can be described according to the WHO-ICF criteria. New developments of functional neurorehabilitation in neurosurgery can significantly improve patients' quality of life (QoL) in terms of both brain and body functioning and certain health-related components of well-being (such as social activities and leisure). Rehabilitation starts with assessment of the functional impairment and the underlying pathophysiology by using all modern diagnostic tools. Our concept of postoperative neurorehabilitation is exemplarily demonstrated in one patient who suffered from acute postoperative locked-in syndrome.

Surgical decompression and fusion were required for post traumatic and recurrent congenital craniovertebral instability at C0–C1. Subsequent functional neurorehabilitation is based on careful planning in accordance with our concept of a holistic *Spectrum of functional early Neurorehabilitation* (Fig. 1) [9, 10].

Keywords: Locked-in syndrome; cranio-cervical junction; post-traumatic; postoperative.

Objectives

Chronic medullar and upper cervical cord compression may exist as a neurologically asymptomatic lesion, exhibiting neither symptoms of cranial nerve impairment nor signs of root compression in the arms. Developmental and acquired craniovertebral junction abnormalities may become symptomatic secondary to compression or ischemia of neural tissue of the brain stem, medulla oblongata and pons. This may happen as an acute indirect impact on a region of the upper brain stem in traumatic brain injury (TBI) and/or traumatic cervical spine injury (SI), [9].

Locked-in syndrome is a distinct diagnosis applied to patients who are typically demonstrating symptoms and signs of alert wakefulness with paralysis of the body and inability to speak but cognitively are relatively intact [1, 9]. Locked-in syndrome is far more likely due to vascular rather than traumatic consequences [5]. Altered level of consciousness, syncope, vertigo, and episodic hemi or tetraparesis as well as facial diplegia and dysmetria may present as neurological symptoms which can be attributed to vascular compromise secondary to repetitive trauma to the vessels, for example, resulting from pathological hypermobility of an unstable atlantoaxial joint [5, 8]. Neurological symptoms and signs attributed to vascular compromise may be manifold and include syncope, altered level of consciousness, episodic hemi and tetraparesis, vertigo, impairment of cranial nerves, and nystagmus. These symptoms may be secondary to repetitive trauma of the spinal cord vessels or intermittent obstruction by angulation or stretching of the feeding arteries resulting from pathologic hypermobility of an unstable atlantoaxial joint [9]. Perilous might be an acute sleep apnoe as well as an unexpected sudden respiratory arrest secondary to local anterior and/or posterior compression of the cervicomedullary junction.

Acute treatment will either be conservative or surgical relying on the underlying aetiology and pathophysiology, and should follow special recommendations. Prognosis depends on the underlying pathology and the time window for medical intervention. Clinical symptoms and signs due to ischemia, secondary to local compression of the arterial and venous blood supply, can be resolved either by conservative treatment with immobilization or following surgical decompres-

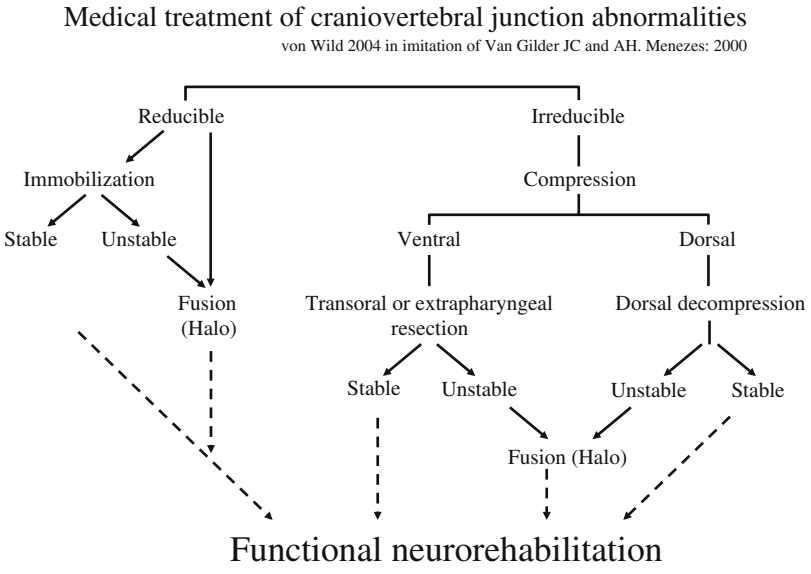

Fig. 1. Algorithm for treatment of craniovertebral abnormalities after Van Gilder and Menzes (Fig. 147-4), modified for functional neurorehabilitation by von Wild (broken lines)

sion by anterior and posterior approach with stabilisation when necessary [9].

Craniovertebral junction abnormalities can be developmental, genetic, or acquired in origin.

They can cause a number of different symptoms and signs, including myelopathy, brain stem, cranial nerve, and cervical nerve root dysfunction; vascular insufficiency or any combination of these.

Medical treatment of craniovertebral junction abnormalities are described in detail elsewhere [9]. The operative procedures have to be tailored for each patient according to the complete assessment of functional anatomy, pathophysiology, and radiological abnormalities. Algorithm for treatment of craniovertebral abnormalities (see Fig. 1) was published by Van Gilder *et al.*; see Figure 141-4 and Table 147-2, pp 38–39 [9]. Functional rehabilitation, following operative procedures with fusion, however, is not specifically mentioned in this context despite the author's remark, "The patient must remain in halo immobilization for 6–12 months after the procedure" [9].

There are insufficient data in the literature regarding neurosurgical rehabilitation in the postoperative locked-in-syndrome; therefore it must be emphasised that in this rare and challenging clinical situation only attendant-led holistic rehabilitation can provide the final and successful result.

Patient and methods

Case report: K.O., a 38 year old man, national of the Arab Emirates, an active soldier in the army of Saudi Arabia for many years, sustained a blunt head injury (HI) when accidentally hit by a tank in November 2001. Following the injury there was an increasing and finally severe tetraparesis with a sensory impairment under C2. Plain roentgenograms (Fig. 2), tomographic studies, and computerized tomography (CT) of the craniovertebral junction revealed a complex abnormality with compression of the displaced cervicomedullary junction. The odontoid process extended more than one half of its length at the Chamberlain's line while the disc C1/C2 persisted. Subluxation of C0–C1 and narrowing of the foramen magnum increased during flexion and extension X-ray investigation; there was a vertebral body bloc C2/C3.

The patient was seen by an orthopaedic surgeon being also a neurosurgeon and expert in craniovertebral procedures, and was transferred to Germany. After careful completion of the diagnosis, including MRI studies (Fig. 2), the patient underwent surgery on December 28, 2001. Obvious congenital instability at C0–C1 required both a ventral and posterior approach for decompression as well as bony fusion of the occiput with the cervical spine. Therefore, as a first step, the upper part of the odontoid was removed by transoral approach which aimed at decompressing the nervous structures for restoration of the vascular supply and functions of the motor and sensory pathways. Subsequently, as a second step, dorsal stabilisation was performed with plates and rods using the Cervifix ®-system and bone grafts which were attached to the occiput and facets. There was postoperative arrest of spontaneous breathing followed by an increasing tetraparesis. In the subsequent postoperative period the patient was left intubated and connected to the ventilator at the intensive care unit (ICU). CT and MRI control studies did not show blood clot or mass lesion in the operative field with instrumentation and bone graft in place. The neurological and cognitive signs and symptoms of an incomplete locked-in syndrome fluctuated

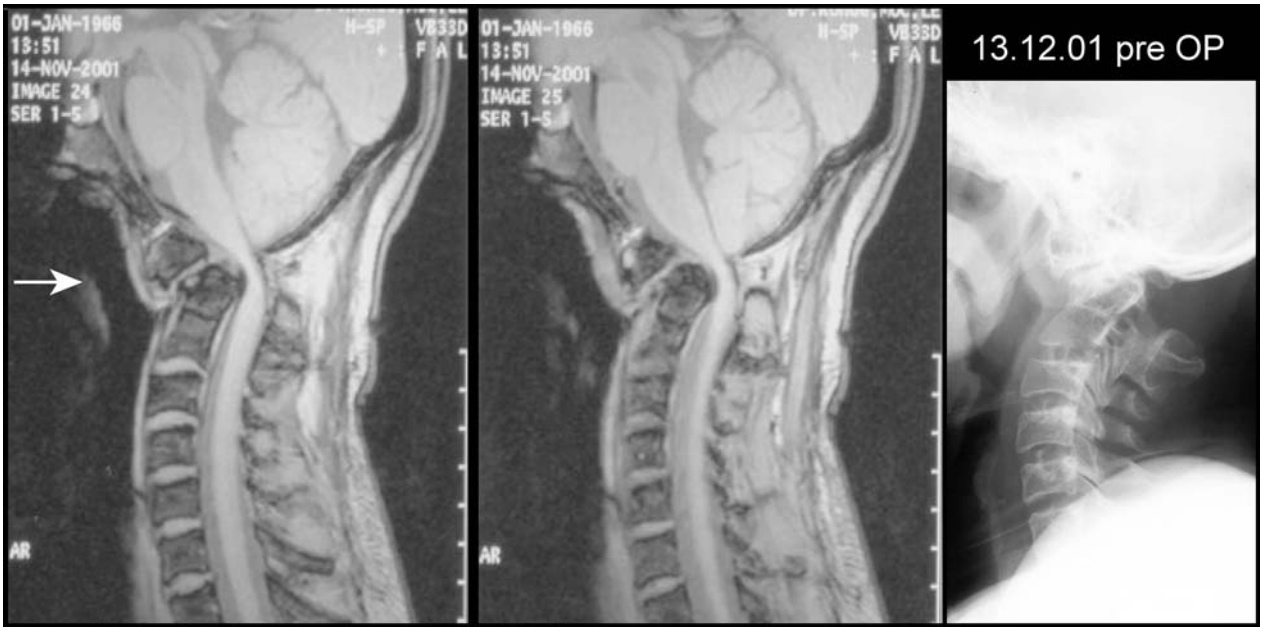

Fig. 2. Sagittal MRI, TSE T2, TR 3500, TE 120 preoperative (14.11.01). Complex congenital abnormality of craniovertebral junction (white arrow) with displacement and local (vascular?) compression of the lower brain stem and upper cervical cord due to bony narrowing of the surrounding space as cause of acute posttraumatic tetraparesis. Plain X-ray (lateral view) shows the bony structures of the anomaly (13.12.01)

so that recurrent intubations and artificial ventilation were necessary to maintain oxygen saturation until the patient finally deteriorated again and became comatose and tetraplegic at the end of the second postoperative week.

He was transferred to our department of neurosurgery for functional early neurorehabilitation not far from the hospital of his primary surgery on January 18, 2002.

As usual neurosurgical rehabilitation was started already in the intensive care unit (ICU) with careful assessment of the underlying pathophysiology. All diagnostic investigations were performed after immediate stabilization of the craniovertebral junction by extension with the aid of the Gardner Wells tongs and tracheostomy. A careful interdisciplinary approach was planned, including all medical specialists and the rehabilitation personnel, taking into consideration the family and his Saudi Arabian background when defining the ultimate goal of neurorehabilitation, i.e. reintegration into a family, society and his reemployment.

Clinical diagnosis was locked-in syndrome, obviously due to vascular compression of the upper and lower brain stem because of postoperative, repeated instability at C0–C1, as it was demonstrated by CT (Fig. 3) and MRI studies. It was waited until partial neurological and cognitive recovery occurred, so that the patient could understand his situation. He was assisted by his wife and our team and especially by the neuropsychologist. However, no improvement in the ongoing complete arrest of spontaneous breathing was seen and also very little change regarding his severe tetraparesis.

A second craniovertebral operation was carried out on January 29, 2002. A dorsal approach was performed again; the bone grafts and the fixateur interne were removed because the screws had loosened (Fig. 3 and 5). A decompression by suboccipital craniectomy combined with an enlargement of the foramen magnum was completed with decompression by laminectomy C1; re-stabilization with the aid of plates and rods of the Vertex® titanium system from the occiput down to C2–C4 at the right and C2–C3 at the left side, combined with wire loops to secure the bone fusion was finally performed (Figs. 4 and 5).

During a subsequent functional neurorehabilitation the patient remained in halo-immobilization (Figs. 6 and 7) from February 11 until May 8. Then we had to take the halo away because of the patient's psychotic and claustrophobic reaction and an urgent wish of his family. With a cervical collar bracing for another 4 months everybody was happy and X-ray investigation of the fusion segments postoperatively demonstrated stable conditions.

Continuous ventilation (Fig. 6) was necessary until January 30, thereafter intermittent ventilation and CPAP was needed for one month. The patient remained in the ICU until weaned off from the home ventilator, which was achieved beginning of March. The postoperative course during intensive care treatment and early rehabilitation was uneventful, as it was thereafter during the following months of functional neurorehabilitation in our specially designed department [10, 11, 13]. Here the same interdisciplinary team took care of him Figs. 6–8 until he was able to wash himself, to eat, to walk with help, until he was fully mobilised in his wheel chair and had no cognitive or behavioural deficits, and so fulfilled the cut-off criteria of Phase B (early rehabilitation) based on his functional assessment with the aid of the Early Rehabilitation Barthel Index (FRB) and Functional Independent Measure/(FIM).

At the end of June 2002 he was admitted for further neurorehabilitation (Phase C and D of the German System for Neurorehabilitation) to the Rehabilitation Centre Bonn Bad-Godeshöhe with distally pronounced tetraparesis and marked muscle atrophy of the four limbs combined with spinal ataxia, but breathing was stable and completely normal again. One and a half years after recovery from locked-in syndrome the patient was seen again. At that time he was completely reintegrated into social life and back to the military service in his country.

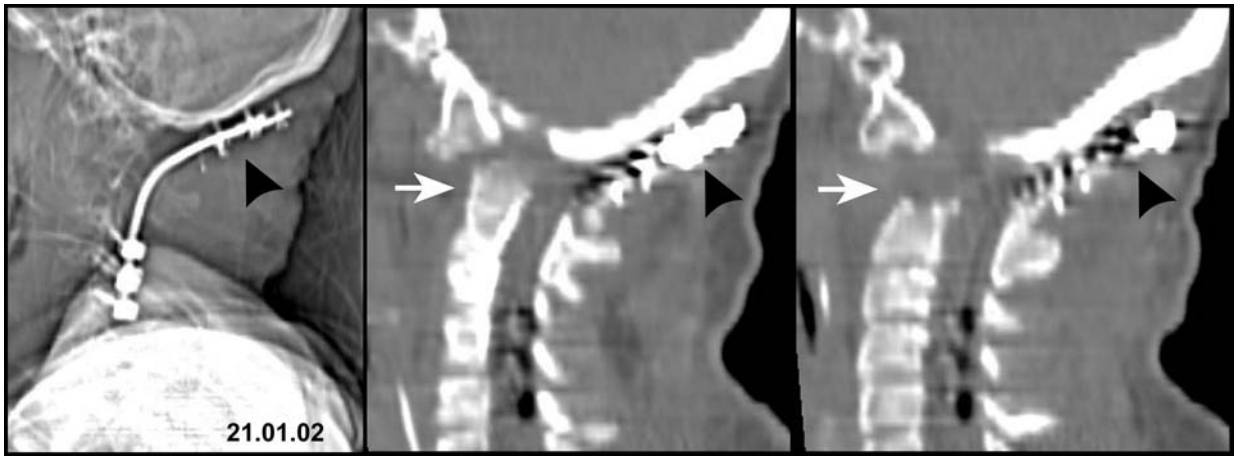

Fig. 3. Saggittal spiral CT and tomograms three weeks after the first operation (21.01.02) to assess the pathology for planning of the surgical procedure as part of correct functional rehabilitation. Black arrows: loosening of the implanted occipital screws and displacement of the fixateur interne (Cervifix R) implants (while patient under Crutchfield's tongue extension because of recurrent instability CO/C1. White arrow: bone defect following transoropharyngeal decompression by nearly complete resection of apex dens axis

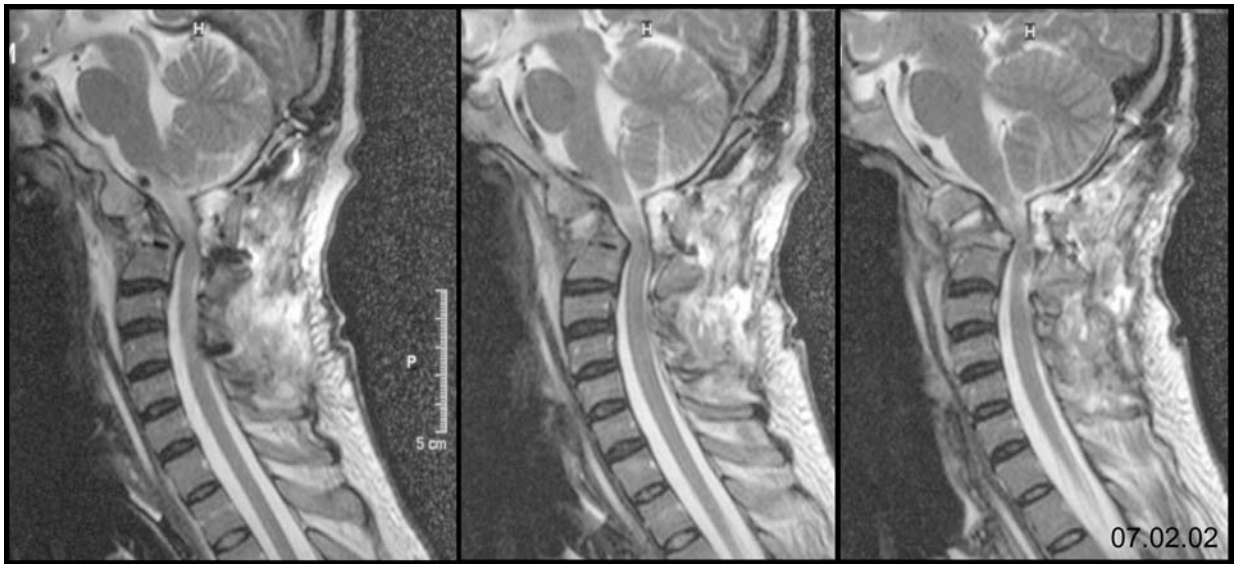

Fig. 4. Postoperative control imaging: Sagittal MRI, TSE T2, TR 3500, TE 120 (07.02.02). Following second surgical dorsal decompression and instrumental stabilization (Vertex R) on Jan 29, 2002. Lateral views showed no acute brain swelling or severe perfusion anomalies in the lower brain stem or upper cervical spinal cord tissue, no additional space occupying clots or secondary haemorrhages, no bony fragments around the displaced CNS structures or within the region of dorsal approach. No signs of CSF fistula after dural graft extension of the cisterna magna. The hook and screws are fixed in place at the occipital bone, cervical fixation hooks C2–C4 and bone graft C0–C3 wired in place as demonstrated on the right side (MRI right side). Head and neck fixed in correct decompression positioning, secured by HALO fixation

Discussion

Locked-in syndrome is a rare postoperative complication. It may occur after HI and SCI when it can be due to compression of the vascular system of the upper and lower brain stem. The primary cause for this may be a congenital malformation of the craniovertebral junction which, after trauma, leads to functional neurological impairment and severe instability. Early functional neurorehabilitation is not usually mentioned in the orthopaedic and neurosurgical literature to overcome and to improve disturbed central nervous functioning. Rehabilitation can reduce secondary complications while stimulating spontaneous recovery

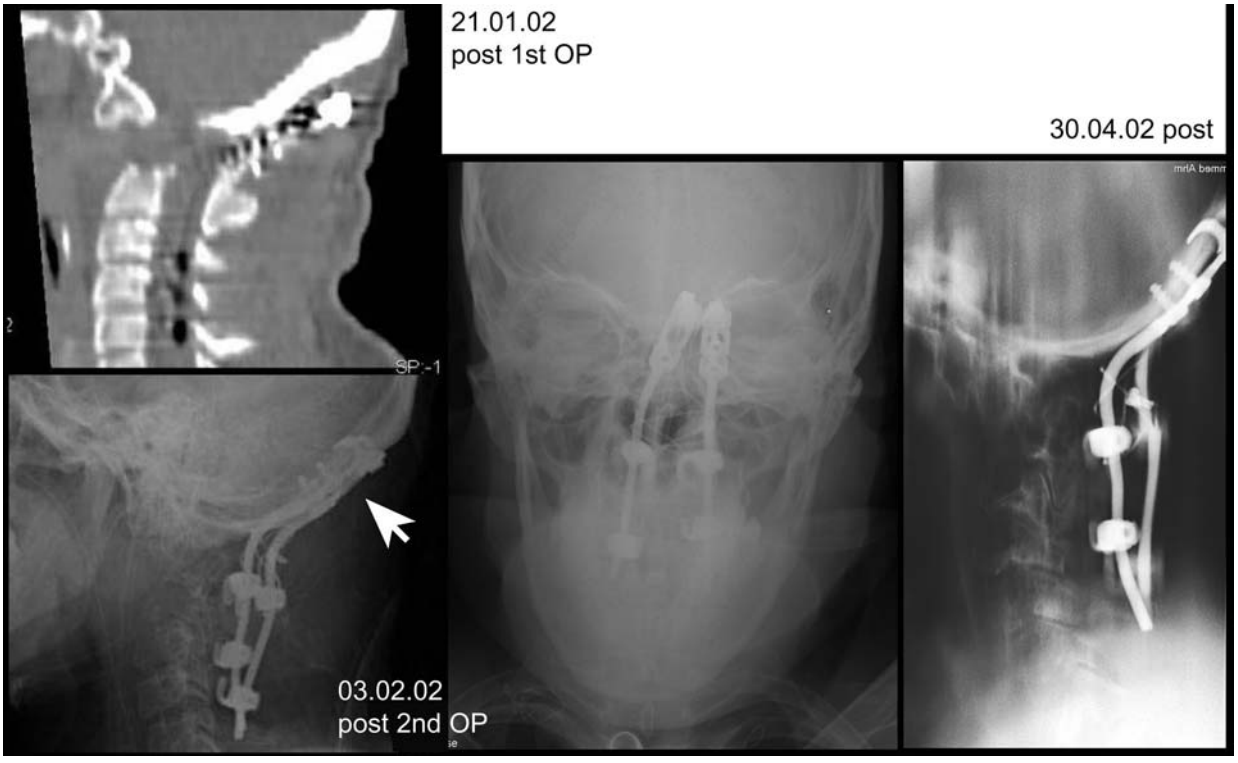

Fig. 5. Sagittal X-ray controls postoperative, anterior-posterior and lateral views (lower left side and middle) on day 5 (03.02.02). Renewed dorsal stabilisation of the craniocervical junction after bony decompression of the occipital bone and C1 because of recurrent instability. Correct positioning of fixateur interne (Vertex R system) concerning occipital hooks and screws (white arrow), rods, wired bone grafts and hooks at C2–C4 right, C2–C3 left side. Head and neck fixed in slight extension while supported in fixateur externe (Halo). Upper side left: in comparison sagittal CT on day 24 after first OP (21.01.02) with loosening of the occipital screws as signs of postoperative instability.

X-ray lateral view (right side) after 2 months: no change with clinically dramatic improvement of neurological and mental cognitive functioning (30.04.02). Screw and hooks are still in perfect place

and supporting restoration which is based on brain plasticity.

Neurosurgical rehabilitation is not a new but a widely forgotten tool. It has an old tradition in Europe and especially in Germany [12]. Our concept is based on early ideas on rehabilitation of sensory motor impairments as formulated by Karl Otfrid Foerster (1873–1941) [3]. It includes therapeutic exercises of peripheral paresis and physiotherapy of central motor disorders, differentiating between spastic and paretic components. In our patient impairment was caused by post traumatic and surgical craniovertebral instability and vascular compression.

Neuropsychological rehabilitation has become an indispensable and major part of functional neurorehabilitation in neurosurgery to help improve the patient's cognitive status, emotional and motivational disturbances as well as psychosocial adjustments following the acute impact lesion of the brain and spinal cord [11, 13]. Our concept of neuropsychological rehabilitation [10], which is an irrevocable part of a modern neurorehabilitation team work, is mainly based on the important studies of Kurt Goldstein [4, 7], Alexander R. Luria (1902–1977) [2, 7], Anne-Lise Christensen [2], and George P. Prigatano [7]. Prigatano quotes: ''The first principle of neuropsychological rehabilitation is that the clinician must enter the patient's phenomenological field in order to sense what he or she experiences. – Therapy aimed at the reducing of patient's frustration and confusion will be eagerly met by the patient (and the relatives), irrespective of whether such rehabilitation activities actually improve higher cerebral functions'' (end of citation pp 28–29, 1999).

Specially designed and equipped departments for early rehabilitation are presently available in Germany where an inter-/multidisciplinary team allows the patient to recover as much as possible at the ear-

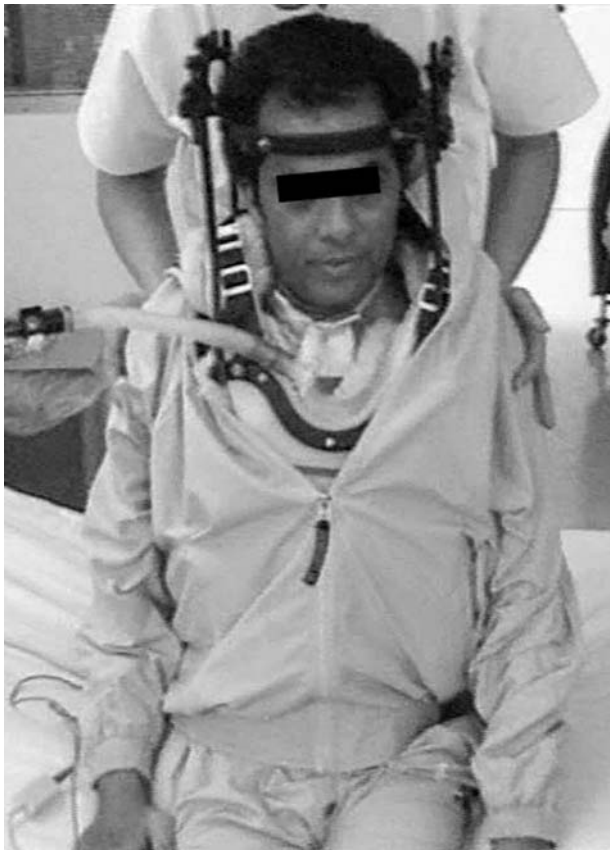

Fig. 6. At the intensive care ward the patient recovers slowly from central coma and functional locked-in syndrome. Here, two weeks after second operation, still severely tetraparetic and artificially ventilated, sitting in a wheelchair during physical therapy in an upright position because of its strong sensory stimulus to CNS (reticular formation and frontal lobes) regarding awareness and spontaneous breathing. Halo fixateur externe to support craniocervical stabilisation

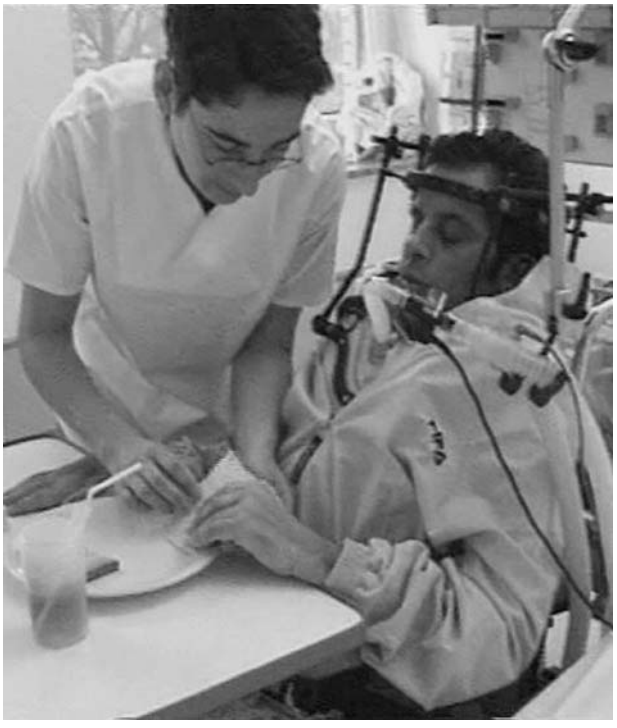

Fig. 7. Active daily living (ADL) training, having meals (here for example breakfast) with the personal occupation therapist (assisted by speech therapist at the back) while still tetraplegic sitting in the wheel chair in upright position at the ICU. Continuous artificial ventilation with ICU respirator via preoperative tracheostomy. "Weaning off" efforts by anaesthesiologists in cooperation with neurosurgeons (third postoperative week)

liest time, starting already in the ICU [11]. Postoperative early rehabilitation in neurosurgery opens up a new venue for restoration of impaired neurological disorders as well as for neuropsychological, cognitive and behavioural functions [2, 7].

Holistic rehabilitation, as we see it today, covers the whole spectrum of neurological-neurosurgical rehabilitation [10]. Rehabilitation has to start right after the impact with careful assessment of the functional impairment and the underlying pathophysiology by using all modern diagnostic tools. If necessary, it is combined with adequate operative procedure(s) and/or intensive care treatment. This has successfully been demonstrated in our case report with complete functional reintegration into social life. The principles have been classified with the aid of the WHO ICF and require that neurorehabilitative treatment starts in a multidisciplinary way which corresponds to our standards for quality management in early neurological-neurosurgical rehabilitation.

Functioning, as defined by the WHO-ICF, serves as an umbrella term encompassing all body functions, activities, and participations in social life (=Quality of Life).

ICF defines components of health and some health-related components of well-being.

These domains are described from the perspective of the body, the individual, and the society in two basic lists: 1. *Body* functions and structures and 2. *Activities* and participation in social life meaning to be mobile and to enjoy social contacts, emotions and play [7, 13].

Conclusion

From the beginning of neurological surgery, preservation and restoration of impaired CNS and PNS

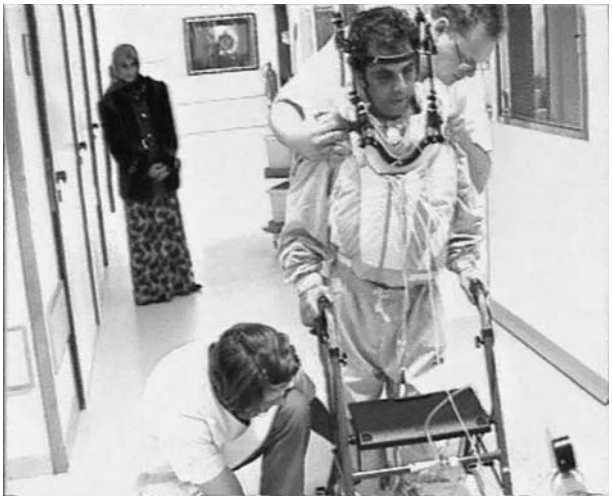

Fig. 8. Physiotherapy, ADL, and neuropsychologic therapy at the ICU four weeks postoperatively. First steps during restoration of locomotion at the floor of the ICU with the aid of a walker and a small battery driven respirator for ambulant ventilation. Spontaneous breathing is still insufficient. One personal physiotherapist and one occupational therapist controlling while supporting voluntary active movement (interdisciplinary team approach). Worth mentioning is the spouse as part of the neurorehabilitation team (in the background). She guaranteed the best personal, social and cultural environment for the mentally and cognitively impaired, emotionally stressed husband during early rehabilitation when he slowly emerged from coma and locked-in syndrome

functions have been the primary task of physicians. This important fact demands that neurosurgeons must get involved with the issues of functional neurorehabilitation. In this context I trust on continuing co-operation with the intensive care physicians, anaesthesiologists, neuro-radiologists and the early neurorehabilitation team as well as with the neurosurgeons from other hospitals of the area as altogether they can be of indispensable help from the very onset of medical treatment for the brain, spine and spinal cord injuries and thus achieve the patient's best functional outcome.

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Treatment options and results in cervical myelopathy

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Summary

Cervical myelopathy is a clinical entity resulting from external compression of the cervical medulla. The clinical course can be divided into the acute form (secondary to trauma) versus subacute (progression within weeks to months) and chronic cervical myelopathy (months to years). The clinical picture of myelopathy is that of unsteady gait with long-tract signs, such as hyperreflexia, spasticity and extensor plantar responses.

Between 1997 and 2000, 359 consecutive patients have been operated on in our department presenting with a variety of symptoms related to compression of the cervical medulla. Beside of standard MRI for all patients we applied SSEPs, gait analysis and dynamic MRI studies as additional helpful tools in evaluating selected patients pre- and postoperatively. We prefer the anterior approach as first-line approach because in the majority of patients the osteophytic spurs are more dominant anteriorly, and after anterior decompression and stabilization the posterior approach appears safer. We also favor the more extended approach of spondylectomy versus multilevel decompression in patients with bisegmental or multisegmental spinal canal stenosis. However it seems to be that radicular decompression is better achieved through multilevel decompression than through spondylectomy.

Keywords: Cervical myelopathy; decompression; fusion; anterior approach.

Introduction

Cervical myelopathy is due to a progressive lesion of the spinal cord at the level of the cervical spine. In the following the definition of ''cervical myelopathy'' is confined to the clinical picture of myelopathy due to external compression of the cervical medulla while differential diagnoses of inflammatory origin, vascular-occlusive disease or intrinsic cord tumors are not considered. Clinical symptoms are usually those of more or less rapidly progressive cervical spinal dysfunction, often a history of previous cervical neck pain or brachialgia can be ascertained. In the following the clinical picture of cervical myelopathy will be summarized, and the radiological evaluation including additional investigations will be presented. Also, the different surgical procedures selected to stop – if possible reverse – the progression of the disease will be presented in a series of patients operated upon in the last years in our department.

Clinical picture

The clinical course of cervical myelopathy can be divided into (i) the acute form versus (ii) subacute mostly progressive form and (iii) chronic cervical myelopathy.

The acute form is usually associated with a history of trauma, often from a car accident, in summer times frequently from diving activity resulting in a whiplash injury followed by a more or less massive neurological deficit ranging from mild paralysis to complete quadriplegia. Particular attention needs to be given to cervical trauma in the presence of ankylosing spondylitis [18].

The subacute form is characterized by a rapidly progressive neurological deficit, often associated with an initial history of cervical pain or brachialgia and subsequently leading within weeks to months to gate disturbance and or other symptoms of myelopathy.

The chronic progressive form differs from that of the subacute progressive myelopathy only with respect to the time frame, i.e. the clinical course may take months to a year to develop and may sometimes be difficult to differentiate from other causes.

The clinical picture of myelopathy is that of unsteady gait with long-tract signs, such as hyperreflexia, spasticity and extensor plantar responses. Because of the subtle development of symptoms, often it is difficult to precisely define the onset of the disease.

Differential diagnoses include, in the acute phase, an

injury to the spinal vasculature which may also occur in the presence of a trauma due to arterial dissection, a spontaneous acute vascular occlusion or an acute inflammatory process can often easily be distinguished by the history of trauma while the differential diagnosis for subacute progressive myelopathy includes rapidly progressive spinal cord dysfunction due to intramedullary or extramedullary tumors, even of rare origin [2, 12]. The clinical picture of slowly progressive gate disturbance in chronic progressive cervical myelopathy may be difficult to differentiate from that of gate disturbances associated with normal pressure hydrocephalus. Another important differential diagnosis is encephalomyelitis disseminata (ED), particularly in the presence of myelopathy sign in MRI. Because of its variable clinical presentation, arteriovenous fistulas with congestive medullary damage always need to be kept in mind in the presence of a fluctuating neurological syndrome.

Since the clinical picture may only indicate a cervical spine dysfunction without giving, initially, the cause of the lesion, additional investigations are warranted. If the clinical picture of spinal cord compression is present, the cause of the compression needs to be clarified. It may be due to osteophytic spurs, ossified posterior longitudinal ligament (OPLL) [11], particularly in Asians, bone tumors, extra- or intradural tumors or even rare causes such as vertebral artery hyperplasia.

Additional investigations

Conventional x-ray may show the course of spinal cord compression in cases of tumor e.g. of metastatic origin presenting with osteolytic lesions, sequelae of trauma and the degree of degenerative disc disease with osteophytic spurs extending both anteriorly and posteriorly.

Computed tomography (CT) has long been the method of choice and is still indicated to obtain good information concerning the osseous stability. With regard to spinal cord compression it often needs to be combined with cervical myelography in order to define the degree of spinal cord compression through defining the CSF space anterior or posterior to the spinal cord.

Magnetic resonance imaging (MRI) is the method of choice, however, when diagnosing dysfunction of the cervical cord, with a variety of sequences and planes. Mostly sagittal and transverse planes are used.

The above mentioned differential diagnosis of ED has to be ruled out in the presence of myelopathy signs. These are high intensity lesions on T2 weighted imaging with a – not always – clear anatomical correlation to the level of spinal cord compression, they are mostly located in the anterior part of the cord, while ED foci are located without any correlation to the level of compression and mostly in the dorsal cross section of the spinal cord.

Somato-sensory evoked potentials (SSEPs) are widely used in the diagnosis and differential diagnosis of cervical myelopathy, however, motor potentials seem more sensitive in this setting [23], particularly also in the follow up; however in our experience they are only rarely indicated in order to support a surgical indication once the clinical picture has been defined. Preoperative SSEP may serve, however, as baseline for intraoperative measuring the potentials in order to prevent any intraoperative cord damage e.g. from hyperextension.

Recently, *transcranial magnetic stimulation* has been applied to better examine the motor pathways [10], also in conjunction with intraoperative measurements [5].

In the following we present our experience in the surgical treatment of spinal cord compression at the cervical level including some additional investigations to better define the approach and the extent of the surgery.

Material and methods

Clinical series

Between 1997 and 2000, 359 consecutive patients have been operated on in our department presenting with a variety of symptoms related to the cervical spine including both cord and nerve roots. Surgical approaches to decompress the spinal canal and thereby the spinal cord are the posterior approach and the anterior approach. In 233 patients, the anterior approach was used for radiculopathy, while it was used, in cervical myelopathy, as a single-level approach in 68 patients and as multi-level approach in 28 patients. In 27 cases, spondylectomy was used for myelopathy, while only in 3 cases a posterior approach was chosen.

All patients presented with the clinical picture of cervical myelopathy, often associated with radiculopathy as well. They were mostly diagnosed already on an outpatient basis using standard MRI, rarely only CT had been performed as single investigation. In those patients, additional investigations were performed as required to establish the surgical strategy. Only in patients presenting with traumatic severe myelopathy, usually the complete diagnostics were performed in our department. This included X-ray and CT scan to diagnose the width and configuration of the spinal canal and obtain information concerning the stability of the cervical spine. MRI scans in a 1.0 T or 1.5 T Siemens MRI scanner were performed routinely in the presence of a (even transient) neurological deficit and persistent pain.

Dedicated MRI investigations

In most instances, the site of compression of the spinal cord is obvious from the sagittal plane on MRI. Mostly hypertrophic osteophytic spurs lead to narrowing of the spinal canal. However particularly in multisegmental or severe spinal canal stenosis, also posterior compression may be present; on the other hand, sometimes an impressive clinical picture is contrasted by a mild compression of the spinal cord as seen in neutral position MRI scans. Therefore, it may be necessary to determine the degree and site of compression by using a dedicated, MRI compatible flexion – extension headholder allowing for MRI imaging in a particualr angle. In this semi-dynamic MRI, additional compression of the cervical cord from ventral osteophytes or from dorsal hypertrophied ligamentous structures during these defined mouvements could be demonstrated, thus defining the indication for anterior or combined anterior and posterior decompression of the cervical spine.

Gait analysis

Although not necessarily helpful in a routine clinical setting, additional information concerning the degree of cervical myelopathy – particularly in mild, early forms – and the effect of spinal decompression can be obtained by gait studies which have been published by Kuhtz-Buschbeck *et al.* [9]. In this examination two methods can be applied: (i) walkway covered with paper in order to study the step length, step width, foot angle, gate velocity and step frequency (cadence). Furthermore duration of stance, swing and double support can be defined through imaging of infrared light barriers and clock with video as well as markers on the shoes. A second method which can be applied in specialized laboratories is the treadmill analysis of walking including motion analysis and EMG pattern. It needs to be considered however that gate on walkway and gate on treadmill may differ in so far as treadmill provides the shorter step length, higher step frequency and higher step width compared to walkway at identical velocity.

Selecting the appropriate approach

Once the final cord compression has been defined with regard to its level and extent, surgical options need to be considered. They consist mainly in the anterior and posterior approach based on the previously described studies [3, 4, 6, 8, 15, 16, 21, 26]. The anterior approach allows for discectomy or removal of osteophytes and is followed or not by interbody fusion. A variety of graft materials [20] have been proposed including artificial disc placement [22]; in our department mostly methylmethacrylate ("bone cement", Sulcem^{R}) in the cases of degenerative disc disease while in trauma cases iliac crest bone graft was preferred followed by anterior plating. If the compression of the spinal cord extends over more than just the disc space, either multisegmental discectomy (MSD) using the above described fusion material or spondylectomy (SE, also named corporectomy) with multilevel radiculo-decompression may be considered, the latter followed by interbody fusion with a variety of interposition grafts such as cages filled with the removed bone chips, tricortical bone grafts harvested from the iliac crest or a combination of both [21]. Posterior approaches include laminectomy and laminoplasty, the latter being favored recently because of its superior stability in the long term follow-up [1, 4, 6, 19, 24, 25]. Similar to Wang and Green [25], we prefer the anterior approach as first-line approach because in the majority of patients the osteophytic spurs are more dominant anteriorly, and after anterior decompression and stabilization the posterior approach appears safer than as first line approach.

Clinical results

A retrospective analysis was performed in 144 patients who had undergone spondylectomy or multisegmental discectomy from January 1995 to March 2001. Most of them are part of the cohort mentioned in the beginning. The demographic statistics are listed in table 1. While the median age of the patients warrants aggressive therapy, one has to be aware that the older patients are up to 85 years old and require special considerations concerning the extent of surgery [17]. A postoperative follow up of 224 $\pm$ 302 days was obtained with clinical follow-up examination.

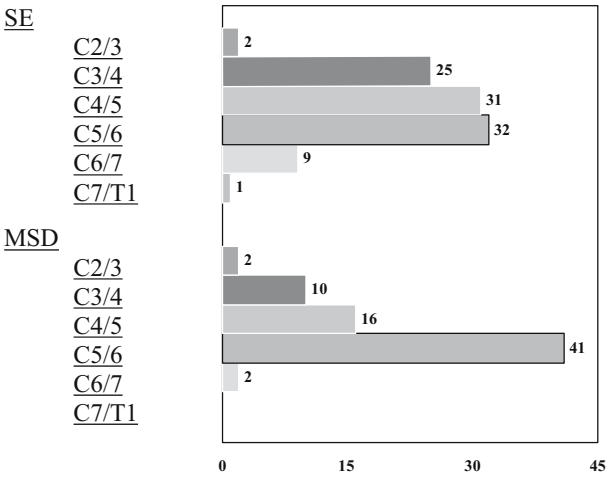
The levels of spondylectomy (SE) and multisegmental discectomy (MSD) are shown in figure 1a,b as well as the etiology of cervical spinal canal stenosis. The preoperative clinical picture is given in table 2. It is obvious that patients with myelopathy were more frequently operated using an extended spondylectomy approach while patients with radiculopathy were often operated upon using a multisegmental discectomy approach. The results of surgery are summarized in table 3. These positive results need to be balanced against the complications which are listed in table 4 and figs. 2 and 3.

In spondylectomy a total of 24.4% complications were noted while in multisegmental discectomy a 11.8% complication rate was obtained. However, the lower number of complications for MSD needs to be related to the fact that in four patients additional surgical interventions were required following MSD before the patient had obtained the best result possible, while after SE no additional therapy was thought necessary.

Using gait analysis in a subgroup of consecutive patients, an significant improvement of gait velocity, step length and step width could be shown immediately postoperatively which was further improved after a longer followup interval. These data have been published in detail [9].

Table 1. *Spondylectomy vs. multisegmental discectomy – patient series*

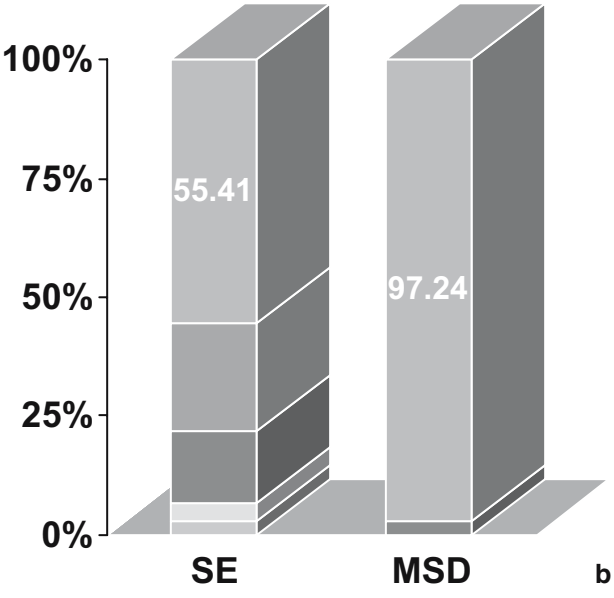
Retrospective analysis of 144 patients January 95 to March 2001
74 spondylectomies (SE), 47 male and 27 female, 55,9 $\pm$ 17,6 years old (max. 85, min. 16)
70 multisegmental discectomies (MSD), 46 male and 24 female, 55,6 $\pm$ 12,3 years old (max. 83, min. 22)
Mean follow up at 224 $\pm$ 302 days postop



	SE	MSD
2 level	20	69
3 level	3	1

SE = 74 MSD = 70

a



b

Fig. 1. (a) Level of spondylectomy (*SE*) and multisegmental discectomy (MSD). (b) Etiology of cervical spinal stenosis, ■ Degeneration; ■ Tumor; ■ Trauma; ■ Infection; ■ Others

Discussion

The results presented here are in wide agreement with those obtained in other clinical series of similar patient populations. Thus they can be used as a guideline for indicating different anterior approaches to the cervical spine and to discuss risks and benefits with the patients. The posterior and the oblique approach to decompress the spinal canal have only rarely been applied in our series, so they will not be discussed further.

From our experience described here we favor the more extended approach using spondylectomy rather than multilevel decompression. However it might be mentioned without precise numbers that it seems that the radicular decompression is better achieved through multilevel decompression than through spondylectomy, in the latter the surgeon being more concerned with the decompression of the spinal canal and not irritating the spinal cord while the lateral intraforaminal decompression may not receive enough attention intraoperatively.

Table 2. *Spondylectomy (SE) vs. multisegmental discectomy (MSD) – preoperative status*

	SE	MSD
	n = 41	N = 68
Myelopathy	22 (53.7%)	13 (19.1%)
Radiculomyelopathy	15 (36.6%)	20 (29.4%)
Ataxia	34 (82.9%)	25 (36.8%)
Paresis	31 (75.6%)	43 (63.2%)
Sensory deficit	36 (87.8%)	63 (92.7%)

Table 3. *Clinical results following surgery: spondylectomy vs multisegmental discectomy – synopsis (first 2 columns for spondylectomy, next 2 columns for multisegemental discectomy)*

	Postop 13 ± 9 d	F-Up 177 ± 175 d	Postop 6 ± 6 d	F-Up 210 ± 327 d
Improvement (%)	78.1	88.6	91.2	80
No change	21.9	5.7	8.8	9.1
Worsening	0	5.7	0	10.9
Further surg decom		0		4

Table 4. *Spondylectomy vs. multisegmental discectomy – complications (N)*

	Spondylectomy	Multisegmental discectomy
Plating	5	0
Infection	1	0
Neurol. deterioration	1	2
Compl. at graft site	2	n.a.
Rec laryngeal nerve lesion	2	2
Medical	3	4
Surgical revision	7	1
Complication rate (%)	24.2	11.8

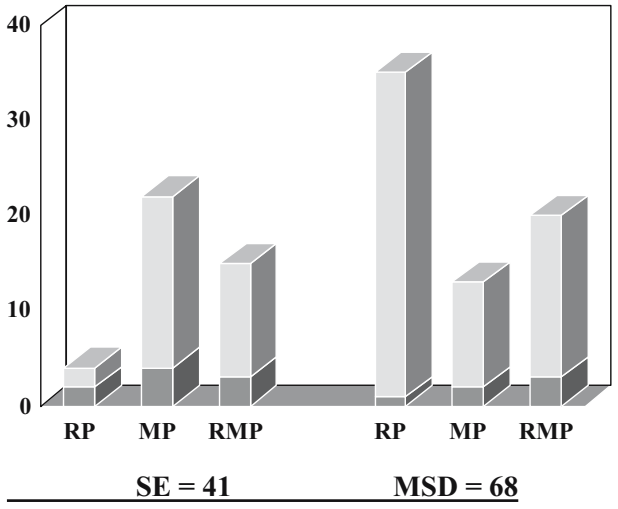


Fig. 2. Postoperative course of radiculo-, myelo- and radiculomyelopathy. *RP* Radiculopathy; *MP* myelopathy; *RMP* radiculomyelopathy, ▫ improved; ■ no change; ▪ worsened

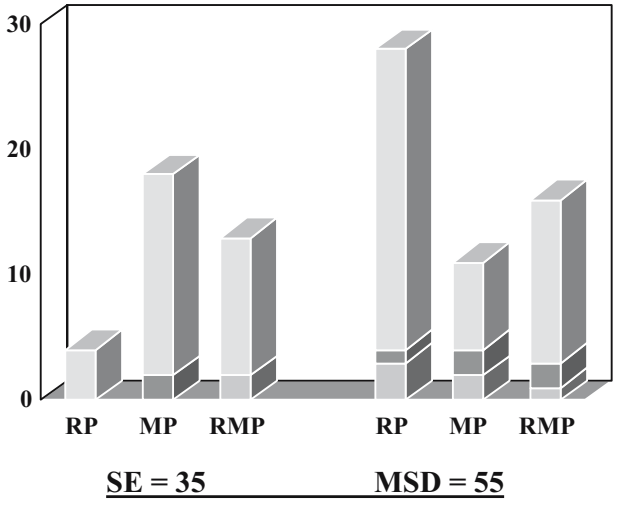


Fig. 3. Long term follow up of radiculo-, myelo- and radiculomyelopathy, ▫ improved; ■ no change; ▪ worsened

While the preoperative MRI evaluation of the patients is essential to determine the optimal approach to the stenotic canal, the detailed gait analysis may also serve as an objective tool for follow-up evaluation of the benefit and detriment of surgery. It has well been shown that gait analyses detected postoperative improvement more sensitively than clinical scores such as that of the JOA [9]. Also, the quality of life should be determined preference-based in these patients in order to better clarify the indication for surgery [7]. However, no long-term study has yet been performed to show the true natural history of cervical myelopathy in order to show benefits and risks for the patient vs. the natural course of the disease.

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The treatment of the sacral pressure sores in patients with spinal lesions

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Summary

Sacral pressure sore treatment requires a multidisciplinary approach, the surgical procedures following nutritional and medical status rehabilitation, spasticity control and sepsis treatment. Serial surgical debridement might also precede flap coverage. Gluteal flaps design such as rotation, transposition or V-Y advancement is selected according to the shape and size of the sore. Our experience with 74 patients with 95 flaps includes 38 rotation flaps, 28 V-Y and 8 transposition flaps. Twenty one patients had bilateral gluteal V-Y flaps. Only 2 transposition flaps had marginal necrosis that healed per secundam. Delayed healing occurred in 12 cases due to sepsis, that healed spontaneously in 10 cases and required surgical re-intervention for excision and flap reposition in 2. Prolonged bed immobilization, postoperative antibiotic therapy and late suture removal are important factors in surgical success.

Keywords: Sacral pressure sore; gluteal flaps.

The sacral pressure sores represent a major problem because of the nursing difficulties of the paraplegic and tetraplegic patients. Even in the best equipped units with nursing staff or in those with beds for anti-pressure sores, some of the patients immobilized in bed will suffer in time from skin ulceration, the most frequent localization being the sacral one, followed by the trochanteric sores.

Among the mechanisms involved in the formation of the bedsores, there are two that have a major importance: the longstanding pressure on the decubitus zones and the friction [5]. To these ones, once the ulceration become visible, the maceration of the intact integument by secretions and the local sepsis will be added [2, 3].

The highest incidence of bedsores develops in tetraplegic and paraplegic patients. 60% of them are tetraplegic patients followed by those with long term alteration of consciousness and by those immobilized in bed due to other medical causes. The old people are more exposed to the risk of the sores due to the skin quality alteration and the circulatory problems.

This paper presents authors' experience in the treatment of the sacral pressure sores in patients with spinal lesions with 3 types of gluteal flaps: V-Y advancement, rotation and transposition.

Materials and methods

For 10 years, between 1992 and 2002, in the Clinic of Plastic and Reconstructive Surgery of the Emergency Hospital, Iasi, we had treated 74 patients with sacral pressure sores whose aetiology is shown in table 1. For those patients, 95 musculocutaneous flaps were performed, in 21 cases the size of the defect required the use of bilateral flaps. The soft tissue defects ranged between 10×5 cm and 20×17 cm.

The preoperative evaluation is fundamental for these patients, the correction of the biological parameters being an essential condition for the treatment success. In all the cases, the correction of anaemia and hypoproteinemia preceded the surgical treatment. A second condition is the control of spastics with para or tetraparesis. If the muscular contractions are too frequent or too intense, the integration of the flap is in jeopardy. For this purpose, the treatment with Diazepam is started preoperatively and continued until healing.

The most important postoperative element is the control of the local infection. Serial microbial cultures have been made in all the cases, and antibiotics have been prescribed according to the antibiogram. Classically, the element that indicates the optimum moment for the operation is the decrease of the microbial density below

Table 1. *The etiology of the sacral pressure sores*

Causes	Number of cases
Posttraumatic paraplegia	28
AVC with hemiplegics	17
Fractures in inferior members	16
Posttraumatic tetraplegia	9
Radionecrosis	4

$10^5/mm^3$, but the clinical aspect of the bedsore can also be an accurate monitoring. Besides the antibiotic therapy, the necrotomy of all the devitalised and infected tissues was obligatory for the sepsis control and that was made at the bedside along with daily dressings in paralytic patients. In the cases where the sensibility was maintained the surgical debridement was made in the operating room under neurolept-analgesia.

The duration of the preoperative treatment was between 5 and 15 days.

Surgical treatment

The vascular anatomy of the gluteal region is well described [4, 11] and it will not be detailed here.

The musculocutaneous gluteal flap was raised as a rotation flap in 38 patients, as a transposition flap in 8, with V-Y advancement in 38 and 2 perforator flaps.

In 21 cases in which the size of the defect required the use of two gluteal flaps, both were identically designed: in 18 cases V-Y flaps and in 3 rotation flaps respectively. In 7 cases, a part of the defect was covered with split skin grafts, but the grafted zone was located outside the area of maximum pressure over the sacrum.

In 17 cases the patients had simultaneous trochanteric pressure sores, unilateral in 9 cases and bilateral in 8, that were covered with other flaps: i.e. 16 flaps of rotation and 9 flaps using muscle-cutaneous fascia. In 6 of the unilateral cases, the trochanteric coverage was undertaken at the same time with the sacral region, taking care to raise the gluteal flap from the opposite side. In the remaining 3 cases, as in all the bilateral ones, the treatment of the trochanteric sores was postponed until the gluteal flaps healed up.

When planning the flap, one should remember that tissue necrosis due to long standing pressure on bony embossments proceeds also from deeper structures up to those superficial, the sore having a cone shape. In consequence, the size of the flap can largely exceed the apparent skin defect.

The choice of the type of gluteal flap depends on the geometry and the size of the defect [12]. A trapezoidal or a triangular form has made preferable the choice of a rotation flap while for the rectangular defects, the transposition and the advancing flaps were preferred. When the width of the post-excision defect was less than 10 cm we used a single flap; when the defect was larger than 10 cm we selected two V-Y advancement fasciocutaneous gluteal flaps.

The gluteal musculocutaneous flap is very reliable, allowing the adjustment of its geometry to the size and shape of the receptor zone.

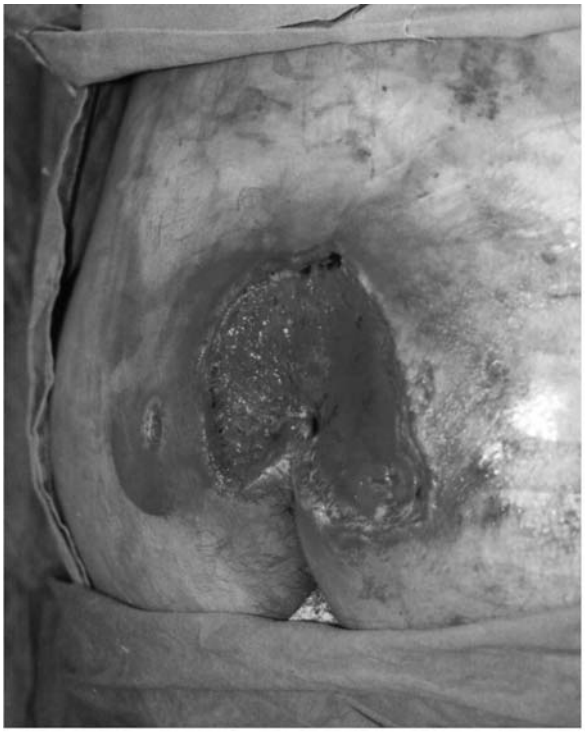
For the *rotation or transposition flaps*, after the incision of the whole circumference we have desinserted the gluteus maximus muscle from the iliac crest to allow medial mobilization [2, 3]. If necessary the distal portion of the muscle can also be incised to allow further mobilization, but it should be avoided in ambulating patients. On the contrary, if less advancement is needed, the muscle origin can be left intact, including in the flap only its superficial fascia. Of the 8 transposition flaps, 4 had the donor zone closed by direct suture (Fig. 1) and 4 requested partial skin grafting.

The musculocutaneous V-Y flaps are drawn in the axis of the gluteus maximus muscle, uniting the posterior superior iliac spine and the greater trochanter [13]. The length of the flap is twice the ulcer size and the width should be slightly larger than the defect (Fig. 2). The dissection starts superiorly and laterally until the gluteus maximus is encountered and proceeds in the space between the maximus and medius gluteal muscles. The origin of gluteus maximus is desinserted from the sacrum and from the posterior iliac crest to achieve the maximal medial advancement of the muscle. The caudal dissection descends down to the gluteus maximus which can be left intact or its fibres can be dissected in the axis of the muscle in order to detach completely a gluteus island. After advancement, the muscle island is secured over the sacrum and the flap is sutured in two layers. Donor site closure is performed with V-Y advancement.

In the fasciocutaneous version of the V-Y flap, the dissection spares the gluteus muscle, but it includes in the flap its superficial fascia [19]. The fascia is raised on each side of the flap but not in the central zone where the main musculocutaneous vessels are located.

For *the perforator flap*: the location of the emergence of the main cutaneous branches of the superior gluteal artery is marked preoperatively at the internal third of the PSIS-GT line [10]. The dissection proceeds similar to the GM fasciocutaneous flap, elevating the muscular fascia until the perforators are encountered. The perforators are dissected by splitting the GM muscle in the direction of its fibers. Reaching the superior gluteal vessels, the pedicle lenght obtained is 8 cm [10, 15].

The V-Y gluteal perforator flap has several advantages: a maximal medial advancement up to 10 cm, no sacrifice of the gluteus maximus, relative simple execution, reduced bleeding and a great mobility of a flap [1].



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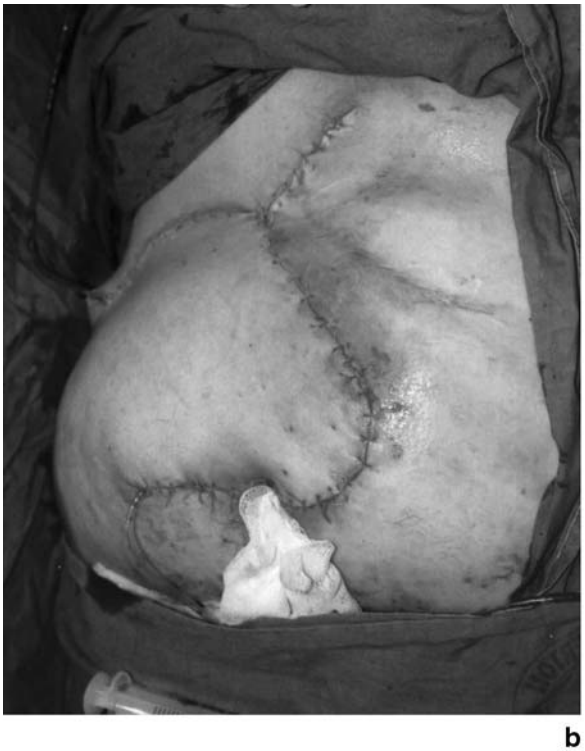

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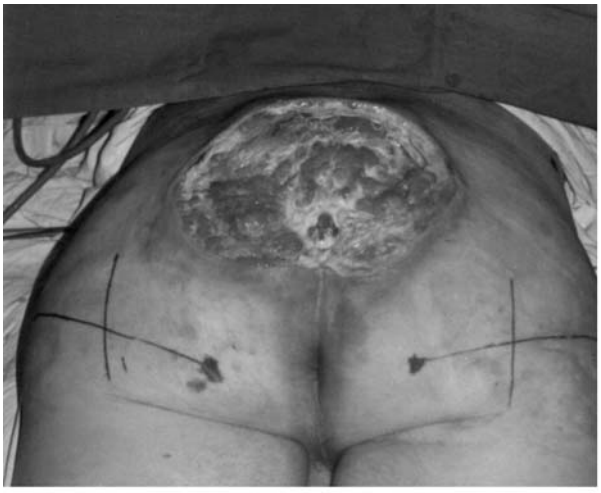
Fig. 1. (a) Preoperative appearance of a sacral pressure sore. (b) Transposition flap moved into the defect



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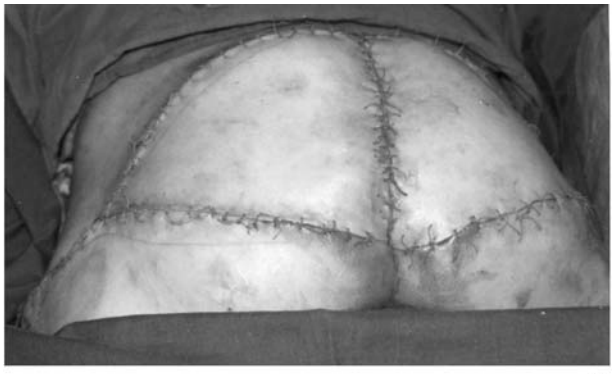


b

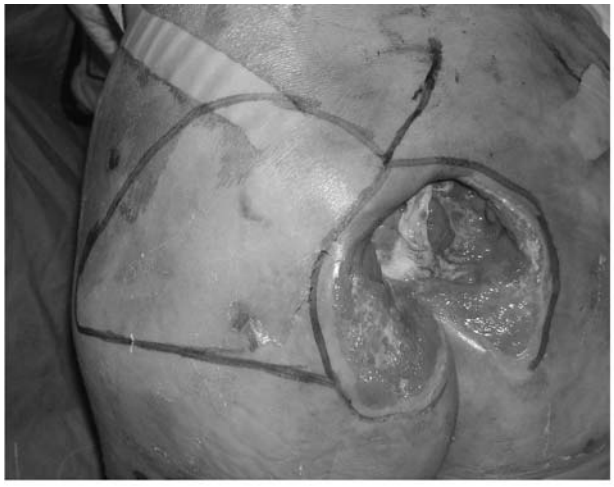
Fig. 2. (a) Large pressure sore. (b) Result after coverage with 2 musculocutaneous V-Y gluteal flaps

In both our cases, the advancement needed was 8–9 cm (Fig. 3).

Results

The postoperative course was uneventful in most of the cases. Only 2 transposition flaps had a small marginal necrosis, less than 1 cm, probably due to the local sepsis or skin tension, that healed up per secundam. The infection delayed the healing in 12 cases but healed spontaneously without further complications in 10 cases and required surgical re-intervention for debridement and flap reposition in 2.

In all 21 cases that could be reviewed distantly over a period of more than 1 year, only 2 had recurrences of the pressure sore, due to poor nursing and altered general state.



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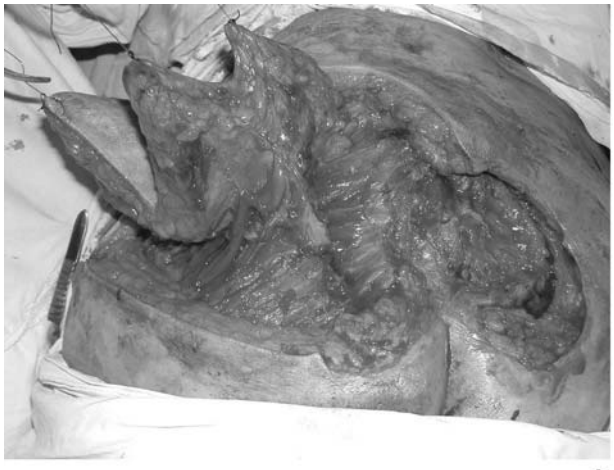

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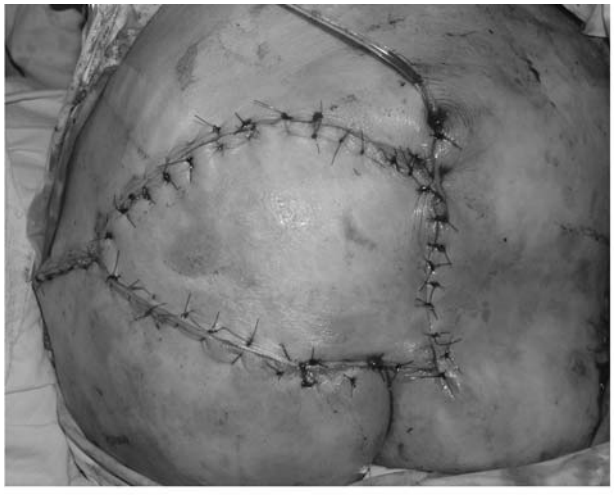

c

Fig. 3. (a) V-Y flap design. (b) Perforator flap raised. (c) Final result

From the 11 cases involving skin grafts over the initial defect or the donor zone of the transposition flaps, only 2 healed without any complications. The remaining 9 patients had partial skin graft loss which healed by secondary intention in 8 cases and required another grafting in one.

Discussions

The large number of sacral sores treated in the plastic surgery departments, and the great amount of material and human resources they required, justify a retrospective analysis of the elements that should be taken into account when approaching such cases.

The first issue that should be outlined is the fact that a multidisciplinary approach is mandatory. All medical and nutritional problems of the patient should be corrected before the local treatment is started [3, 8]. Special attention should be paid to the control of spastics because uncontrolled movements lead to the delay of the flap integration on the recipient site and to wound dehiscence. The control of the local sepsis should be more rigorous than in the case of coverage of skin defect of other aetiologies due to the lower resistance and reactivity of such tarred patients.

In our opinion, the temptation to use skin grafts to cover defects caused by pressure sores should also be rejected even in the case of patients with superficial tissue losses (2nd degree) or when the granular tissue would seem ideal for grafting. We consider that skin grafts should not be used for coverage of sacral pressure sores, because they do not have sufficient mechanical resistance for a supporting area. The graft take is almost always partial due to a poor recipient bed, a too early support on the grafted area or sepsis. Even when healing is obtained after serial grafting, the high recurrence rate does not justify the effort.

The only valid solution in the treatment of sacral sores remains the flap covering. The planning of the re-constructive method should go from simple to complex, so that reserve methods are kept in case of failures or sore recurrence.

Simple fascio-cutaneous flaps are a reliable option in the case of pressure sores because they keep at their basis the source of the loco-regional vascular supply represented by perforator vessels coming from the superior gluteal artery. They have the advantage of a simpler operative technique, but their mobility is lower and they offer less sacral padding than with the musculous-cutanous flaps. We used only rotation or

transposition flaps, but Limberg flaps have the same qualities [8]. In our opinion, the technique of splitting the gluteus muscle [5] adds only an excess of operative time and bleeding with no real advantages in comparison with the fascio-cutaneous flaps.

The introduction in the therapeutic arsenal of musculo-cutanous flaps by Maruyama [10] opened the perspective of the successful treatment of great or recurrent sacral pressure sore treatment. It has two primordial advantages: the safety of vascular supply provided by the constant perforators from the superior gluteal artery and the good mechanic protection of the supporting areas provided by the gluteus muscle.

The patients with medullar lesions don't have the same restrictions of mobilization the gluteus maximus compared to those who have the perspective of walking again and standing. This is a benefit, because the bony embossment can be better protected by the muscular body, giving to the whole flap a greater mechanical resistance. The only disadvantages of sectioning and mobilizing the gluteus muscle is an increase of the operative time and the greater bleeding that has to be compensated by transfusions. The maximal mobilization of the gluteal musculo-cutanous flap in its classic variant is about 5–7 cm, so that for larger pressure sores two flaps are required.

The V-Y perforator flap artery provides maximal medial mobilization and avoids the need for bilateral flaps and of grafting the donor area in the case of large sized defects. Its fascio-cutaneous variant leaves the muscular body in place, which also makes it useful and harmless for non-paralytic patients. The presence of the gluteal fascia gives a higher quality coverage of the sacrum in comparison with the simple cutaneous flaps without sacrificing the muscle.

The dissection of the perforator branches of the superior gluteal artery introduced by Koshima in 1993 [7] exploits the entire length of the flap pedicle, which enables a medial mobilization of 10 cm without tensioning the pedicle. Another advantage is the possibility of rotating the whole cutaneous island with approximately 90°, which allows a better adaptability to the shape of the recipient area.

The versatility of the gluteal flap allows the coverage of the sacral pressure sores with various shapes and sizes, the larger defects imposing the use of bilateral flaps. Regardless of the technical variant, their complete and uncomplicated integration requires the strict observance of some postoperative principles: prolonged immobilization until complete healing, postoperative protective antibiotic therapy at least 5 to 7 days and late suture removal.

In conclusion, the gluteal flap is the method first intention for the coverage of the sacral pressure sore both in paralytic and non-paralytic patients, with an accessible surgical technique, a great freedom in designing the flap and a low recurrence rate due to a good quality of the skin.

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D. Neurological-neurosurgical-neurobehavioral rehabilitation

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Phenomenological aspects of consciousness – its disturbance in acute and chronic stages

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Summary

The meaning of a disturbance of consciousness is completely different in an acute as opposed to a chronic stage. In the acute stage, the grade of arousal is the most essential component in order to assess the changes of the level of intracranial pressure in neurosurgical emergency room. A new coma scale called Emergency Coma Scale has been proposed, which represents a combination of the Glasgow Coma Scale and the Japan Coma Scale.

In the chronic stage, however, contents of consciousness or mental function deserve phenomenological and holistic investigations, keeping the difference between consciousness and mind in consideration, in order not only to treat and care for patients following cerebral injuries, stroke and mild cognitive impairment in aged people. We propose the difference in conception between consciousness and mind; that is, consciousness consists of psycho-sensory afferent system, mind of psycho-motor efferent and afferent system, and memory and language as liaison officers between them. This proposal would play a role to understand mental change in the natural aging processes, when memory and cognition are deteriorating gradually, but is still in evolution in the field of culture.

Keywords: Consciousness; disturbance of consciousness; acute stage; chronic stage; GCS; Japan Coma Scale; Emergency Coma Scale; mind.

Introduction

There is a need to clarify the definition of consciousness in the field of neuroscience and philosophy. However, the purport of a disturbed consciousness in clinical practice is completely different comparing acute and chronic stage. This should be clarified and solved to treat and care properly for patient with disturbed consciousness in both emergency period and during subsequent rehabilitation.

In an acute stage of a disturbed consciousness, grades of arousal are the most essential components of the assessment of intracranial deterioration to achieve proper timing for decompression craniotomy. On the other hand, disturbance of contents of consciousness presents a main theme in the chronic stage. At the same time the polyphasic sleep/wake cycles are very important at this stage, because frequencies of the cycles mean the grade of the feedback to the ARAS from the damaged higher cerebral structures. Therefore, the cycles relate negatively to the degree of recovery of the higher cerebral structures. In the chronic stage, there is no emergency situation in which craniotomy has to be performed, while the patient's ADLs are more important matters. Then, coma scales consisting of multiple axes are needed in the chronic stage, while a coma scale in the acute stage should be simple and straightforward on one axis.

Glasgow Coma Scale (GCS) and Japan Coma Scale (JCS)

GCS was proposed in 1974, and since then it prevailed all over the world. GCS is expressed as total score of eye opening, verbal and motor responses, from 3 to 15 in 13 grades. Curiously enough, JCS (Table 1) was independently proposed in the same year, 1974 in Japan, and it is still very popular and widely used in Japan, even in a TV drama. JCS is divided into 3 levels according to the grade of arousal; that is, awake spontaneously, can be aroused, and not arousable. Each level is further divided into 3, then 10 grades as a total including 0 in clear consciousness.

Each of GCS and JCS has their own advantages and drawbacks. The advantage of GCS is that the term "arousal" is not used, which is occasionally difficult,

Table 1. *Japan Coma Scale**

- *One–digit code*: The patient is awake and:
  JCS – 1: almost fully conscious
  JCS – 2: disoriented
  JCS – 3: unable to recall name and date of birth
- *Two–digit code*: The patient is able to be aroused by
  JCS – 10: speech
  JCS – 20: painful stimuli
  JCS – 30: only repeated painful stimuli
- *Three–digit code*: The patient is not aroused by painful stimuli, but responds with
  JCS – 100: localizing
  JCS – 200: slight movements
  JCS – 300: none

* Neurosurgery (Tokyo) 2: 623–427, 1974

Table 2a. *Proposal of Emergency Coma Scale**

- *One–digit code*: The patients open their eyes, speak, and/or behave spontaneously (awake), and
  ECS – 1: can say correct date, place, and person.
  ECS – 2: can not say correct date, place, and/or person.
- *Two–digit code*: The patients can open their eyes, speak, and/or behave (aroused) by
  ECS – 10: speech
  ECS – 20: painful stimuli
- *Three–digit code*: The patients can neither open their eyes, nor speak by painful stimuli (not aroused), but respond with
  ECS – 100L: localization
  ECS – 100W: withdraw forearm with opened armpits
  ECS – 200F: flex forearm with closed armpits
  ECS – 200E: extend forearm with closed armpits
  ECS – 300: none

* Proposal from Japan Neurological and Neurosurgical Societies (2003)

even for medical staff to understand its meaning correctly. On the other hand, there are a few drawbacks; there are 120 combinations at 13 levels, which mean multiple scores in one level, hard to memorize for the layman, 3 components can not rarely be summed up, and difference between normal withdrawal and abnormal flexion is extremely difficult [4]. In case of JCS, eye opening with a blink is used as a substitute of arousal, and therefore, one score can be selected at one level, except in a very rare instances of a severe face trauma or eyelid ptosis. Further, the level of severe grades is divided only into 3 digit code. As far as a coma scale is concerned in emergency set up, we should realize that almost all accidents occur outside hospital; at home, on the road, or at office, where there is no medical staff.

Proposal of Emergency Coma Scale

CT shows the location and the size of the intracranial lesions, but it does not necessarily suggest ''the level of emergency''. For instance, we do not care much about urgent management so long as the patient is awake, while we really worry whether or not we need to treat the patient as emergency when he or she is prone to be drowsy. Therefore, we absolutely need to judge whether or not the patient is alert or wakeful with or without impending herniation.

Considering these details, we propose ''Emergency Coma Scale (ECS)'' as a coma scale in an acute stage of disturbed consciousness, which is the combination of GCS and JCS (Table 2a). ECS suggests the intracranial situation in 3 stages, without using ambiguous terms like arousal. ECS functions like a traffic signal.

Discussion

The application of ECS is simple and easy to memorize without employing difficult terms such as abnormal flexion, and therefore, always can be assessed by the same score among the medical staff or layman. Further it can be used in any situations, such as in patients who are intubated, with tracheostomy, or in aphasics and even in people who do not speak the local language. ECS is now being investigated by both the Japan Neurological and the Neurosurgical Emergency Societies [3]. The only point of concern in ECS is that larger numbers mean the more severe grade. However, this is not a great problem, because it is transferred in reversal in each country according to their practice (Table 2b).

As far as coma scale in the chronic stage is concerned, we should clearly define the consciousness and the difference between consciousness and mind. Henri Ey [1] remarks in his book, entitled ''the consciousness'', that consciousness should be neither reduced to wakefulness, nor assimilated into the ''highest level'' such as reflective and creative thought, and he confessed that the problem of consciousness is formidable, and it is understandable why so many writers prefer to deny consciousness so as not to have to define it. On the contrary, in the process of explaining the oriental philosophy, Toshihiko Izutsu [2], one of the greatest philosophers in Japan, has tried to renounce and replace mind, which is a key term in Buddhism into modern consciousness in intercultural semantics.

I would humbly like to refer to my working hypothesis on consciousness and mind. Human mental

Table 2b. *Proposal of Emergency Coma Scale Score*

– The patients open their eyes, speak, and/or behave spontaneously (awake), and
ECS – 11: can say correct date, place, and person
ECS – 10: can not say correct date, place, and/or person
– The patients can open their eyes, speak, and/or behave (aroused) by
ECS – 9: speech
ECS – 8: painful stimuli
– The patients can neither open their eyes, nor speak by painful stimuli (not aroused), but respond with
ECS – 7: localization
ECS – 6: withdraw forearm with opened armpits
ECS – 5: flex forearm with closed armpits
ECS – 4: extend forearm with closed armpits
ECS – 3: none

function in a psychosomatic being is the super-system, which is integrated with consciousness defined as a psycho-sensory afferent, and mind as a psychomotor efferent/afferent systems. Briefly I can say that input system is consciousness and output system is mind. However, their relationship is like two sides of the same coin. Memory and language play an important role of a liaison officer in both conscious and mental functions. This proposal is my tentative thinking process to solve one of the perpetual aporia in philosophy and psychology, and never offers the final answer. Input and output to the brain are similar to a computer system, but basically different in the point of a narrative-based medicine (NBM).

In many medical journals we often find the terms such as post-stroke or posttraumatic dementia. However, according to my hypothesis, I do not think these concepts are not used correctly, but they represent simply a disturbed consciousness in the chronic stage, as a continuation from the acute stage, because so-called demented patients suffer from not only cognitive, but also emotional and motivational dysfunctions. Further, vascular depression seems to me to be either a secondary or reactive psychosis, following disturbances of the cognitive consciousness and somatic system, or a primary psychosis with normal consciousness. Transit syndrome [5] is a kind of example.

The damages of the higher cerebral structures are either localized or diffuse in different severities. Therefore, there should be different kinds of pathogenesis of mental dysfunctions.

We can say that common aged person who vividly remembers the summit of his life is a kind of handicapped person, whose sensory organs become deteriorating, and his memory functions only temporarily, even if he is not classified into category of dementia. However, his mind has not deteriorated, but rather continues to progress in depth of experience. We have to think about equal happiness in both young and aged people. For that purpose, we have to orientate human's mental life once more in near future. Economy and science are not all for our happiness, but a human should be happy in holistic lives, when he faces to death.

Actually mind needs consciousness, but consciousness does not need mind, if a human seeks for materialistic happiness as an economic animal. Generally speaking, people are now forced to be average, if they want to get more money, because it is absolutely necessary for a capitalist that a human becomes in average as workers at the same time as consumers. Surely I am neither a capitalist nor a communist, but I am a human who wants to live as I want, and also not to bother anyone.

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Table 2b. *Proposal of Emergency Coma Scale Score*

– The patients open their eyes, speak, and/or behave spontaneously (awake), and
ECS – 11: can say correct date, place, and person
ECS – 10: can not say correct date, place, and/or person
– The patients can open their eyes, speak, and/or behave (aroused) by
ECS – 9: speech
ECS – 8: painful stimuli
– The patients can neither open their eyes, nor speak by painful stimuli (not aroused), but respond with
ECS – 7: localization
ECS – 6: withdraw forearm with opened armpits
ECS – 5: flex forearm with closed armpits
ECS – 4: extend forearm with closed armpits
ECS – 3: none

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Neuropsychological experiences in neurotraumatology

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Summary

My work in Neurotraumatology was initiated in 1961, when I as a neuropsychologist got a position in a neurosurgical University department. The tasks were to evaluate the mental state of patients, give advices to family members regarding the mental and social prognosis of the patients and to support nurses in the initial care of the patients. Initially the methods that were made use of were tests developed by the German neurologist Kurt Goldstein [8] and traditional psychometric tests, but it was not until the theories of A. R. Luria and his investigation method were applied that a true position as a member of the treatment team was secured. Reading Luria's book "Higher Cortical Functions in Man" [9] made me aware of his theories. The skill to perform the investigation was acquired during visits to Luria's laboratory at the Bourdenko Neurosurgical Institute in Moscow in the nineteen-seventies. Text and material to "Luria's Neuropsychological Investigation" was published in 1974 [1].

The early work was further stimulated by the development in the neurosciences regarding brain plasticity and brain repair [6] and experiences from visits to rehabilitation centres in the US, Yehuda Ben-Yishay's center at New York Medical School, George Prigatano's centre at the time in Oklahoma, and Lance Trexler's center at Community Hospital, Indianapolis led in 1985 to the establishment of the first post acute rehabilitation center in Europe: the Center for Rehabilitation of Brain Injury (CRBI) at the University of Copenhagen, DK [2]. The main program was a holistic day program, six hours a day for four months in accordance with the university semesters, and an eigth months follow-up. Groups of 15 persons started together, collaborating in smaller groups. The present director of the CRBI is neuropsychologist Frank Humle.

A thorough follow-up of the patients' state and improvement through the course of treatment towards social integration, including getting back to work was performed, and studies have indicated that successful integration of the traumatized patient is possible, provided that an early intensive care is succeeded by a comprehensive, individualized post-acute rehabilitation program, of which follow-up is a part, all within the frame of multidisciplinary collaboration.

Keywords: Brain function; neuropsychology; neurotrauma; neurorehabilitation.

Introduction

Recognizing the 1st AMN World Congress, this presentation will focus on the concept of brain function as the specific contribution of the neuropsychologist as part of the multidisciplinary collaboration in Neurotraumatology.

Historically, the integration of neuropsychology into the neurosurgical arena goes back to the World Wars of last century, when early surgical treatment of the wounded soldiers became possible placing demands for continued treatment and effective rehabilitation [11].

Later the tremendous accelerations of traumatic accidents all over the world caused by the industrial and transport development placed heavy demands on neurosurgery. Traumatology, dealing with one of the most costly societal diseases, became an essential part of neurosurgery. Treatment of the functioning of the brain was mainly referred to physical medicine and neuropsychology was only sparsely included.

The first neurosurgeon in Denmark showing deep interest in the brain functioning of his patients was Richard Malmros, professor at the University of Århus. After discharge from his department, patients were followed half a year, and again examined one and two years after their traumas, causing the need for neuropsychological assistance. As the first clinical psychologist in neurosurgery I was given the opportunity to follow patients through intensive to sub-acute care, and later in the post-acute stages with the purpose of making neuropsychological evaluations of their functioning.

The theoretical background for my initial work were practices developed by the German neurologist Kurt Goldstein [8] and the tests generally used were traditional psychometric tests. The reports did not cause much interest or discussion in the daily work in the department; results were noted for their long term information but were of no use in the treatment of the

patients. It was not until A. R. Luria's theory and methods were introduced that a true exchange of knowledge and ideas became possible.

Methods

The neuropsychological findings provided by the investigation according to Luria's theory are described in a terminology, based on knowledge of brain structure and physiology and as such they are immediately applicable in the treatment of the patients. Furthermore, the implied phenomenological approach and feed back principle inherent in the investigation method has a reassuring effect on the patients. Awareness and insight are improved, and emotional reactions diminish. As a consequence of this, use of the method also had a positive effect in the contact with the patients' relatives.

An example shortly after the introduction of the method was the reaction during the neuropsychological investigation of a 15 year old young man, run down by a car on his way home from school, whose agitated behavior caused problems for the nurses. In relation to the investigation he made a drawing, which illustrated his feelings of anxiety and his need of reassurance. For him the understanding of his anxiety and the meeting of his need had an immediate effect on his agitated behavior.

According to the basics of the theory, the higher psychological processes represent complex functional systems, which are social in their genesis, mediated by language and conscious in their performance. The concept of function is equivalent to complex functional systems distributed in broad areas in the brain. The functional system is the collaboration of specific, cortical & subcortical elements, ensuring the operation of the functional system. From this follows that brain function cannot be localized in specific areas of cerebral tissue, but is distributed in a constellation of cooperating zones of the cerebral cortex and the subcortical structures.

Voluntary movement is an example of a functional system in which different cerebral structures participate in an integrated and complex way. Depending upon which structure is damaged, the functional system will be characterized by a specific disturbance. The affected structure can be identified only after the symptom(s) have been analyzed in detail. According to classical neurology, disturbances of voluntary movement (apraxia) correspond simply to lesions in the parietal and antero-parietal areas. However, the more accurate analysis demonstrates not only that the structure of voluntary movement is extremely complex, but also that such movements involve the integrated participation of more than one brain structure.

Basic elements of the functional structure of voluntary movements are 1) the kinesthetic afference (i.e. the combination of kinesthetic signals concerning muscle tone, joints, etc., of the limbs in movement); 2) the synthesis of visuo-spatial afference (i.e., the combination of signals relating to the spatial coordinates of the limbs); 3) the kinetic organization (i.e., the consecutiveness and the "melodic synthesis" of the movements); and 4) the intentional aspect (i.e. the goal). Controlling these elements of voluntary movements involve various cerebral structures: the sensory areas of the postcentral cortex, the parieto-occipital areas, the basal ganglia and the premotor area, and the frontal lobes, respectively. Different disturbances of voluntary movements (i.e. different forms of apraxia) occur, depending on which of these areas is damaged; they can be differentiated diagnostically to kinesthetic apraxia, spatial apraxia, kinetic apraxia, and intentional apraxia. Accordingly, the disturbed elements will be evidenced in all other functional systems of which they are part.

In the Luria procedure neuropsychological functions are investigated according to a theory, purporting to analyze the defects qualitatively instead of formally and quantitatively. Also an analysis of the factors underlying the behavioral manifestations is performed, which makes the interpretation of the findings a logical conclusion of the theory.

A case history concerning a 59 year old man may illuminate the specific course of treatment, planned in accordance with his individual needs and in this case the available possibilities. The outcome turned out successfully, three years after the injury, his held back license was returned to him and he reestablished himself in his business. The patient, an independent accountant, was injured during a vacation in Switzerland, where he fell down 30 meter; he was picked up by a helicopter and brought to a nearby hospital. His GCS was seven, he was multitraumatized, had a cranial fracture, a pelvic fracture and pneumothorax.

The initial treatment provided by the Swiss hospital was effective; his family was invited to participate in the care and in three weeks he had improved so much that referral to a neurosurgical department in DK was possible. On arrival he was confused and slightly agitated, with lack of insight in his condition, tried to get out of his bed. CT scan was repeated and showed contusion and a right hemisphere frontal haematoma. After five weeks in the department where the patient only occasionally felt at ease, he was discharged to a rehabilitation hospital, where he was mainly given physical treatment.

Due to personal acquaintance the follow-up took place in accordance with the CRBI's treatment procedures, where training of cognitive functions was combined with feed back information and support, given to the patient and the family, the patient gradually regained a realistic insight, which made it possible for him to take up work, although in the beginning at a lower level. Experiences of failure as well as success were discussed during treatment hours strengthened his insight and lead to statements, showing his frustrations and the strength he was able to mobilize in his attempts to overcome them. Coming to terms with his insecurity, accentuated by his sensitivity to the reactions of people, who still seem to mistrust his abilities, has been the most difficult for him to handle.

The specific qualitative analysis of the functioning of the patients inherent in this methodology makes it possible to identify the disturbed functions but also to clarify the means by which the patient is trying to cope with the problems he or she experiences or is presented with, as well as the way he or she is making use of any intact functions in those compensatory efforts. Whether a disturbance is primary or secondary can be decided and the implications of injured areas discerned.

The insight, the application of the theory provides and deepens the understanding of the contribution of the various brain structures. It may be useful in relation to neuroimaging findings and it may be of importance to the neurosurgeon when decision about the possible surgical intervention has to be made.

The advantages with respect to neurorehabilitation turned out to be of importance. Knowledge in detail of the functioning of the patients opens possibilities for better planning of rehabilitation programs, individualized for the specific patient, focusing on intact elements of the functional systems in the rebuilding of new functional systems. As control examinations, imaging techniques in the form of the rCBF investigation as developed by Niels Lassen and David Ingvar, were made use of, first with Niels Lassen in Denmark, later with Jarl Risberg at the University of Lund [3].

Results

The application of the Luria method and the consequences in the treatment and rehabilitation of traumatic patients in the early stages of their improvement

combined with visits to already established centres (Yehuda Ben-Yishay's center at New York Medical School, George Prigatano's centre in Oklahoma and Lance Trexler's centre in Indianapolis) in USA created the background for rehabilitation planning at the Center for Rehabilitation of Brain Injury (CRBI) at the University of Copenhagen.

The establishment was made possible by a private grant, awarded for three years and immediate contact was taken to hospitals and public social authorities. Research had to be initiated alongside with the program planning in order to secure continued interest and economic support.

Data from the first study published [4] originated from 46 moderately to severely brain-injured patients, treated during the CRBI's first three years from 1985 to 1988. Due to control of spontaneous recovery, patients at that time were not admitted until three years after their injury. The program lasted four months with an eight months follow-up. The data concerned social factors such as living conditions, work situation, and leisure activities and showed the four points in time: pre-trauma, pre-rehabilitation, post-rehabilitation, and one year after graduating from the program. Half the patients were traumatic brain injury patients. The results were socially convincing: Living conditions were normalized, one patient who was in a nursing home at the start of rehabilitation lived at home with his wife, dependency was reduced, the younger persons had moved away from their parent's home, more than 70% returned to education or work, and leisure activities reached pre-injury level. The general improvement was present at the one year follow-up, most of it evidenced during the year after commencement.

A study regarding costs was carried out for twenty patients rehabilitated in the year 1987 [10]. An independent research institute was invited to evaluate the costs over a $3\frac{1}{2}$ year period. The 20 patients, who were rehabilitated 1987, showed improvement in quality of life and the public costs were reduced.

Table 1. *The costs before, during and after the treatment at the center*

Time Period	Costs per month per person (DKK)
Before treatment	11,630
During treatment	5,331
Just after treatment	5,843
1 year after treatment	7,802
3 years after treatment	3,675
Reduced costs in the whole period	−190,400

Mehlbye J, Larsen A (1994) Social and economic consequences of brain damage in Denmark: a case study. In: Christensen AL, Uzzell B (eds) Brain injury and neuropsychological rehabilitation – international perspectives. LEA, Hillsdale, New Jersey.

Discussion

The influence of the theory and methods of A. R. Luria at the neuropsychological work at the CRBI has lead to convincing results. By way of research, conferences and publications information has been made available [12]. Neurorehabilitation in many countries has, however, been implemented under difficult conditions. Qualification of function has not been given the sufficient attention, neither in the acute care nor in post acute rehabilitation that is needed in order to secure quality of life for those who sustain brain injury.

In the later years a development that seems promising is evidenced. New trends, originating in neuroscience open for a dialogue between the medical and psychological professionals. Individual variability in brain structure and function has been stressed by Edelmann and Mountcastle [5] and new visions re-

Table 2. *The development in the total public expenditure after 5 years*

Costs	Expenditure after $3\frac{1}{2}$ years (DKK)	Expenditure after 5 years (DKK)
Saved public costs	−190,400	−280,800
Additional expenses for transfer payments	+500	+500
Total saved public expenses	−189,900	−280,300
Center payments	+211,200	+211,200
Changes in public expenses	−21,300	−69,100

Note + = additional expenses; − = savings.

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garding the mind/brain relationship are ventured by Joaquin Fuster [7], stimulated by A. R. Luria's initial work.

To quote Fuster: "My ultimate objective is to substantiate the correlations between a neural order and a phenomenal order, the isomorphism of cortex and mind. Essentially, this is an agenda of practical dualism that, in my opinion, allows us to get as close as we can by experiment to the unity, indeed identity, of the two. It is a difficult and ambitious agenda. It is also an exciting one . . .

The ideas that are defended, again with his own words: 1) cognitive information is represented in wide, overlapping, and interactive neuronal networks of the cerebral cortex; 2) such networks develop on a core of organized modules of elementary sensory and motor functions, to which they remain connected; 3) the cognitive code is a relational code, based on connectivity between discrete neuronal aggregates of the cortex (modules, assemblies, or network nodes); 4) the code's diversity and specificity derive from the myriad possibilities of combination of those neuronal aggregates themselves; 5) any cortical neuron can be part of many networks and thus of many percepts, memories, items of experience, or personal knowledge; 6) a network can serve several cognitive functions; and 7) cognitive functions consist of functional interactions within and between networks."

The task to incorporate these ideas in the examination of brain injury and the interpretation of the patients' function is right in front of us in the service of combined effort from neuroscience and neuropsychology in helping the brain-injured person to regain or rebuild functional networks that can assist in living the saved lives.

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Team care in ICU – Psychotherapeutic aspects and taking care of family of patients with traumatic brain injury

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This talk initially was entitled "Psychotherapeutic aspects in the ICU and taking Care of Family of Patients With Head Trauma". In the meantime the title has shrunk to "Team Care in ICU". My intent today is not to talk solely about the care of patients with head trauma by medical team consisting of neurotramatologists, nurses, physical therapists and other professionals. I would like to share some thoughts with you on the interdisciplinary care in the sense of the medical team treating patients with severe traumatic brain injury and caring for the patient's family.

For many years the coauthor was a nurse at the intensive care unit (ICU) of the Department of Neurosurgery in Graz, who completed a degree of education and trained in psychotherapy, focusing on logotherapy and existential analysis (V. Frankl). With this background she changed much in the way patients are now cared for in the ICU. Her training, knowledge and psychotherapeutic approach still influence the way we carry out work in the unit which I am conducting.

Most of the patients in the ICU are unconscious or in a state of altered consciousness. The unconsciousness seems easy to define in medical terms. But incessant new facets of consciousness and unconsciousness make it almost impossible to define a person in his completeness and unity. As a result, consciousness and unconsciousness have different meaning to different people, based on personal experience and knowledge. We always find it a little hard to begin from the fact that a person who we classify as unconscious is a person like you or me. And if we begin from the assumption that the unconscious person has no mental capabilities, we see no sense in addressing these mental faculties. Minimal movements or expressions remain unnoticed. We deny the unconscious person any capability to feel or experience. But beginning from the hypothesis that the unconscious person is a deficient entity that feels nothing and realizes nothing and just lies there lifeless has dire consequences for the interaction.

Only if we see the person as a holistic entity with a range of levels of consciousness and corresponding abilities to feel and to express himself, and only if we adjust to his level of communication, will we be able to interact with him.

Critical care medicine symbolizes the possibility and stands for control. This can lead to unrealistic and overdrawn expectations which we cannot meet. The working environment is tense, the threat of an alarm is ever present. There is a demand for success and danger of failure. The ICU is seen as an elite unit, but is often slightly mistrusted by the remainder of the hospital. The nursing staff is under psychological and physical pressure. The emotional and spiritual aspects of care is often delegated to the female nurses (probably because we expect a maternal caring instinct of them). We can communicate with the unconscious patient only if we are aware of our own weakness, needs and fears.

In the acute phase of severe head trauma our attention is focused on saving the patient's life. The acute phase begins at the accident site and continues through a transport to the medical center. In the acute phase the paramount priorities are saving the victim's life and preventing secondary cerebral lesions due to elevated intracranial pressure, hypoxia and hypercapnia. This requires careful monitoring and appropriate surgical interventions. Surgical measures frequently require interdisciplinary consultation among

neurosurgeons, ophthalmologists, ENT specialists and faciomaxillary surgeons. Many injuries require carefully planned interdisciplinary treatment, and successful surgery requires an experienced and a competent team. Such medical teamwork has become routine in the neurotraumatologic centres.

Furthermore, I want to talk about the difficulties and issues involved in communicating with the family members of the patients after head trauma. All of us know that the presence of a family in the ICU can cause organizational and interpersonal problems. These problems are the result of the family perceives the ICU observation & understanding how operates. Particularly in the initial phase of the critical care, the family is confronted with the situation for which they are not prepared. The unexpected news of life-threatening injury of a loved one can elicit a wide variety of reactions from emotional shock and denial on one hand to agitation, anxiety and disorientation on the other. Between these almost archetypal reactions there lies emotional devastation at the impending loss of a loved one.

But while the medical critical care apparatus is geared toward stabilizing and saving the injured person, the family is often isolated, disoriented and alone. The infrastructure of the hospital seldom takes the family's needs into account. Waiting areas for ICUs are often unkind and impersonal and lacking in areas providing privacy. They are certainly not areas designed to help family members beginning to cope.

Sometimes the behavior of the hospital staff conveys to a family that the fight for the patient's life is hopeless. Families have to wait, and every minute that goes by deepens their fears.

When the family members are let in to visit the patient they are not prepared for what they see. The patient is unconscious and intubated and attached to an array of monitoring and infusion devices and catheters. Apart from the shock there is a sense of distance. The patient is not the person they used to know. They are worried for the loved one and crave for information. They want to know about the chance for survival, the diagnosis, treatment and the prognosis. The quest for information is the first step in coping with the situation, and in this phase the medical team of physicians, nurses and therapists has to be coordinated. The manner in which information is provided conveys to them the health & their loved one. The family can thus be integrated into the ICU environement and the relatives begin to gain perspectives for the future.

The prognosis is obviously a central issue in discussions with the family. If the prognosis is unfavorable the reactions are similar to those of family confronted with dying patients. The process of grieving often takes place in stages, of which denial is the first. The phase of denial, which is a form of protection to the acute situation, frequently gives way to a phase of aggressive behavior. The family is both burdened with the patient's life-threatening condition but it is also expected to provide love and support for the patient. This tension not infrequently results in aggressive behavior directed at the medical team.

The last phase of the family's reaction is acceptance, resignation or depression. If therapeutic efforts are unsuccessful and the patient may die the family has to learn to grieve and to accept. The optimism by the medical team in this situation is perceived as alienating. The technology of the ICU is frightful. Not infrequently the fear that the patients has been degraded to an object of medical technology leads the family to see death as deliverance.

The family of patients who do well react differently. The family feels accepted by the ICU staff, they trust the treatment team and respect their efforts to save the life of their loved one. But even in this situation careless and uncoordinated actions can disrupt the relationship between the family and the treatment team. The result can be manifest distrust or the threat of legal action. In any case the ICU's reputation can be thus affected.

It is clear that the entire ICU staff – physicians and other team members – need to communicate with the family sensitively and astutely as well as competently manage the care of the patient. Despite the considerable clinical demands on ICU teams, we need to step up to the social and emotional challenge which keeps occurring during a treatment of patients with TBI.

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Early clinical predictive factors during coma recovery

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Summary

In severe brain injury patients few studies have examined the role of early clinical factors emerging before recovery of consciousness. Patients suffering from vegetative state and minimally conscious state in fact may need variable periods of time for recovery of the ability to follow commands. In a previous study we retrospectively examined a population of very severe traumatic brain injury patients with coma duration of at least 15 days (prolonged coma), and we found, as significant predictive factors for the final outcome, the time interval from brain injury to the recovery of the following clinical variables: optical fixation, spontaneous motor activity and first safe oral feeding. Psychomotor agitation and bulimia during coma recovery were also favourable prognostic factors for the final outcome. In a further study, also as for the neuropsychological recovery, the clinical variable with the best significant predictive value was the interval from head trauma to the recovery of safe oral feeding.

In the present study the presence of psychomotor agitation diagnosed by means of LCF (score 4 = confused-agitated) at the admission time in rehabilitation predicted a statistically significant better outcome at the discharge time in comparison with patients without agitation.

Keywords: Traumatic brain injury; prolonged coma; outcome; predictive factors; psychomotor agitation.

Introduction

Survivors from severe traumatic brain injury (TBI) often suffer from prolonged disturbances of consciousness, such as coma (lasting from few hours to some days), prolonged coma (lasting at least 15 days), minimally conscious state [12] and/or vegetative state [16]. These conditions may be followed by different clinical outcomes, with recovery process lasting variable periods of time (from few days to several months). Age, severity and duration of coma, duration of post-traumatic amnesia, site and extent of cerebral lesions and association with polytrauma and hypoxia have been considered as the main prognostic factors to predict the outcome of severe TBI patients [1, 5, 10, 17–19]. Unfortunately, useful studies looking at a variety of clinical features observed in the early phases of coma recovery are scant. The majority of the studies investigating the clinical factors predicting the final outcome of severe brain injury patients regard the acute phase. In fact, coma severity, measured by means of Glasgow Coma Scale (GCS) [22], is correlated with the final outcome, assessed by the Glasgow Outcome Scale (GOS) [15], although it is well known that the GOS score may still change within the first year from brain injury. Coma duration is also a significant predictive factor for final outcome of severe brain injury patients, but few studies have examined the role of early clinical factors emerging before the complete recovery of consciousness. Patients suffering from vegetative state and minimally conscious state in fact may need variable periods of time for recovery of the constant ability to follow commands. The duration of post-traumatic amnesia, which is a significant prognostic factor for final outcome of TBI patients, is very difficult to be measured in minimally conscious state or patients suffering from persistent memory disturbances.

In a previous study we retrospectively examined a population of severe traumatic brain injury patients with coma duration of at least 15 days (prolonged coma), in order to evaluate some possible clinical predictive factors for the final outcome. A statistically significant correlation with disability scales such as GOS and Barthel Index (BI) at 1 year follow up was found for the time interval from brain injury to the recovery of the following clinical variables: optical fixation, ability to follow commands, spontaneous

Table 1. *Post-Coma Scale (1–60)*

Pupils
4 = bilateral prompt reaction
3 = monolateral prompt reaction
2 = torpid reaction
1 = mild signs of reaction
0 = no reaction – fixed mydriasis

Reaction to auditory stimulation
4 = obeys to command
3 = looks toward the stimulation
2 = blinks in response to the stimulation
1 = does not look to the stimulation
0 = no reaction

Reaction to painful stimulation
4 = finalized motor response
3 = localizes, but not ward off pain
2 = decorticated reaction
1 = decerebrated reaction
0 = no reaction

Eyelid and ocular bulbi position
4 = eyes open spontaneously
3 = eyes open to stimulation
2 = eyes open to painful stimulation
1 = fixed divergence of the bulbi
0 = eyes closed

Motility of the eyes
4 = ocular pursuing
3 = blinks to menace
2 = absent oculocephalic response
1 = present oculocephalic response
0 = pendular movements of the eyes

Oral movements
4 = normal (follows commands)
3 = bite tendency and oral exploration
2 = trismus, jaw contracture
1 = primitive oral automatism (jawning, sucking, bruxism, etc.)
0 = no oral movements

Spontaneous motility and posture
4 = normal
3 = spontaneous motor activity
2 = decortication
1 = decerebration
0 = flaccidity

Speech
4 = normal
3 = aphonia or dysarthria
2 = confused and stereotyped words/confabulations
1 = incomprehensible sounds
0 = no speech

Behaviour
4 = appropriate interaction
3 = psychomotor agitation
2 = spastic crying and/or laughing
1 = antagonistic behaviour
0 = no psychomotor initiative/inertia

Communication with the environment
4 = verbal
3 = by gesture or writing
2 = by eyelids closure
1 = by mimic reactions
0 = absent

Duration of consciousness disturbance (at the evaluation time)
4 = less than 1 month
3 = less than 3 months
2 = less than 6 months
1 = less than 1 year
0 = longer than 1 year

Breathing
4 = normal
3 = tachypnoea or stertorous
2 = with pauses/periodic breathing
1 = intubation/tracheostomy
0 = assisted ventilation

Feeding
4 = normal
3 = dysphagia
2 = food refusal (incostant feeding by mouth)
1 = stomach tube/gastrostomy (PEG)
0 = parenteral nutrition

Sphincters' control
4 = normal
3 = sporadic incontinence and/or retention
2 = urine condom/napkin
1 = vesicostomy/intermittent catheterization
0 = no control (permanent urine catheter and fecal incontinence)

Cutaneous trophysm
4 = normal
3 = small non infected bedsore
2 = wide non infected bedsore
1 = infected bedsore or multiple bedsores
0 = multiple wide and/or infected bedsores

motor activity and first safe oral feeding. Psychomotor agitation and bulimia during coma recovery were also favourable prognostic factors for the final outcome [8].

In a further study we evaluated the possible role of some clinical factors in predicting cognitive outcome in a group of TBI patients, with GCS lower than 8 and prolonged coma. The clinical variables evaluated in correlation with the neuropsychological outcome were the following: age, duration of unconsciousness, duration of post-traumatic amnesia, interval from head trauma to neuropsychological evaluation, interval from head trauma to recovery of oral feeding, and

finally interval from head trauma to first verbal communication. The clinical variable with a significant predictive value on most neuropsychological scores was the interval from head trauma to the recovery of safe oral feeding. Length of unconsciousness and the time interval between head trauma and both first verbal communication and oral feeding were negatively correlated with the global measure of disability as expressed by the GOS score in the expanded version [9].

Clinical observations have suggested that traumatic brain injury patients go through a stage of agitation and restlessness as a natural part of recovery process [2–4, 21]. Moreover, psychomotor agitation and restlessness are reported as favourable prognostic features of recovery from severe brain injury [2, 21].

Aim of this study was to confirm the possible prognostic role of some clinical factors emerging during recovery of consciousness in severe brain injury patients with prolonged coma, such as the presence of psychomotor agitation, for predicting the final outcome.

Materials and methods

We enrolled 150 severe brain injury patients, consecutively admitted to the Rehabilitation Hospital Santa Lucia in Rome, from October 2001 to October 2003, as in- or out-patients. The collection of data was performed to join in a multicentric Italian study on severe acquired cerebral lesions (GISCAR), involving 66 rehabilitation centres for severe brain injury.

At the admission to our Rehabilitation Hospital (t_0) and at discharge (t_1) the following disability scales were administered to all patients:

- Levels of Cognitive Functioning (LCF) [14];
- Disability Rating Scale (DRS) [20];
- Glasgow Outcome Scale (GOS).

In order to obtain a single "improvement index" (I.I.), LCF, DRS and GOS were summed up and normalized, to make the interval between scores homogeneous for the 3 scales. In particular, since DRS has a total range score of 30, LCF of 8 and GOS of 5, LCF was multiplied for 3.75 ($8 \times 3.75 = 30$), whereas GOS was multiplied for 6 ($5 \times 6 = 30$). I.I. was finally obtained by the difference of the normalized sums of the 3 scales at t_0 and t_1 times.

In a minority of patients (30 patients) Post-Coma Scale (PCS) [7] (Attached) was administered at admission to our Rehabilitation Hospital by two blind examiners, to correlate PCS with DRS and to evaluate the inter-rater reliability of PCS. Correlation between the 2 examiners (PCS1 and PCS2) and the 2 disability rating scales was examined by means of Spearman R test. P level was set up at 0.05.

Finally, age, etiology of coma, interval from coma to admission in rehabilitation and the presence of psychomotor agitation during coma recovery were investigated in correlation to the outcome at discharge from rehabilitation.

Statistical analysis of the data was performed by means of non parametric tests such as Kruskal-Wallis, Fisher exact test and by logistic analysis.

Results

Among the 150 severe brain injury patients admitted as in-patients, day hospital or out-patients, 80 in-patients at the first rehabilitation admission were examined.

The 80 patients (57 M, 23 F) had a mean age of 38 years (range: from 18 to 78) and a mean coma duration of 29 days (range: 2–180 days). The etiology of brain injury was: traumatic brain injury (TBI) ($N = 51$ patients; 63.8%); hypoxic coma ($N = 8$ patients; 10.0%); hemorrhagic stroke, including non traumatic subarachnoid hemorrhage ($N = 17$ patients; 21.2%); ischaemic stroke ($N = 2$ patients; 2.5%); cerebral infections meningo-encephalitis ($N = 2$ patients; 2.5%). The mean length of stay, including the whole period of rehabilitation (as in-patient, day hospital, out-patient) was of 161 days (range: 23–519 days).

Among TBI patients ($N = 51$) only 5 patients (9.8%) were older than 50 years and none of them had a significant improvement, i.e. improvement index (I.I.) higher than the median score. Conversely, among patients younger than 50 years (90.2%), in 28 patients (60.9%) the improvement was statistically significant (Table 2). Patients younger than 40 years had a probability to improve higher (about six times) than patients older than 40 years, with a trend to a statistically significance ($p < 0.06$).

As for the etiology, the improvement index (I.I.) of traumatic patients was higher than non traumatic cases (15.7 vs 11.2), with a trend to statistical significance ($p < 0.09$) (Table 3).

Table 2. *Improvement index as related to patients' age*

Age	Improvement index		Total (%)
	Improvement	No improvement	
<50 years	28 (60.9%)	18	46 (90.2%)
>50 years	0	5	5 (9.8%)
Total	28	23	51

Table 3. *Comparison between improvement index from traumatic (TBI) and non traumatic brain-injured (non-TBI) patients*

	Patients observed	Total I.I.	Mean	Variance	Std Dev
TBI	51	801.50	15.71	139.71	11.82
Non-TBI	29	326.25	11.25	79.97	8.94

$p < 0.09$ – Fisher exact test 0.0868.
$p < 0.02$ – Fisher exact test 0.014.

Table 4. *Comparison between Improvement Index in TBI patients with LCF score = 4 (confused-agitated) and TBI patients with LCF scores different from 4 (not agitated)*

	Improvement index		Total
	Improvement	No improvement	
LCF = 4	15 (71.4%)	6	21 (41.2%)
LCF non 4	13 (43.3%)	17	30 (58.8%)
Total	28	23	51

$p < 0.05$ – Fisher exact test 0.043.
LCF Level of Cognitive Functioning.

Table 5. *Improvement Index as related to time interval between TBI and admission at rehabilitation*

Interval TBI/rehabilitation	Improvement index		Total (%)
	Improvement	No improvement	
<90 days	22 (68.8%)	10 (31.3%)	32 (62.7%)
>90 days	6 (31.3%)	13 (68.4%)	19 (37.3%)
Total	28	23	51

$P < .001$ – Fisher exact test 0.0107.

Among the 51 patients, 21 (41.2%) had an LCF score equal to 4 (confused-agitated) at admission in rehabilitation and among them a statistically significant higher percentage of patients showed an improvement index (I.I.) higher than the median score (equal to 13) ($p < 0.05$).

Therefore the presence of psychomotor agitation diagnosed by means of LCF at the admission time (t_0) predicted a statistically significant better outcome at the discharge time (t_1) in comparison with patients without agitation (Table 4).

As for interval from brain injury and admission in rehabilitation, the beginning of rehabilitation within 90 days significantly increased the improvement probability of about 5.7 times ($p < 0.02$) in comparison with patients admitted in rehabilitation later than 90 days after brain injury (Table 5).

This result was also confirmed by a logistic analysis including the different clinical factors, i.e. age, interval from brain injury to admission in rehabilitation and coma duration.

Finally, PCS, as a measure of global disability, including also the interval from coma to the evaluation time and the presence of bed rest syndrome, showed a good inter-rater reliability and a statistically significant correlation with the DRS score (Table 6).

Table 6. *Correlation between two disability rating scales*

–	Spearman R	p-level
PCS 1st–PCS 2st	0.96	0.001
DRS–PCS 1st	−0.88	0.001
DRS–PCS 2st	−0.92	0.001

1st First Examiner, *2st* Second Examiner, *PCS* Post-Coma Scale, *DRS* Disability Rating Scale.

Discussion

Vegetative state is usually defined as "the absence of any understandable response to external stimuli or inner need" [16]. However, such a definition raises the question of whether psychomotor agitation represents a lack of response to external stimuli or inner need. Restlessness and agitation in the first phase of coma recovery, or as behaviour emerging in severe brain injury patients with prolonged disturbances of consciousness, rarely leads to a significant functional interaction of the patient with the environment. Usually, in fact, the agitated patient does not follow commands, either for antagonistic behaviour or for extreme attention lability. Is therefore psychomotor agitation a minimally conscious state or a vegetative state? As a matter of fact, in spite of the lack to follow commands, restlessness and agitation may be interpreted as purposeful behaviour and might precede the recovery of consciousness.

In this preliminary study the presence of psychomotor agitation at the beginning of rehabilitation was a good predictive feature for recovery at the end of rehabilitation program.

Other behavioural disturbances have been previously reported in severe brain injury patients, such as Klùver-Bucy syndrome, i.e. presence of 3 or more of the following symptoms and signs: increased oral activity, hypersexuality, hypermetamorphosis (extreme attention lability), memory disorders, placidity, loss of people recognition, bulimia [13]. The syndrome has also been reported as a possible recovery phase and positive prognostic feature for a good recovery in patients with severe traumatic brain injury and prolonged disturbance of consciousness [6, 11].

In a previous study [8] we also demonstrated the positive predictive role of some clinical features emerging during recovery of consciousness in very severe brain injury with prolonged coma, for the final outcome, i.e. time interval from brain injury to the recovery of optical fixation, spontaneous motor activity

and the first safe oral feeding. Moreover, as previously reported, in very severe brain injury patients with prolonged coma, also the neuropsychological outcome was best predicted by the time interval from brain injury to the recovery of the first safe oral feeding [9]. Psychomotor agitation and bulimia were also favourable prognostic factors for the final outcome [8].

As for spontaneous motor activity, it is a common clinical experience that patients with preserved spontaneous motor activity had better outcome than patients with pathological posturing of upper and lower limbs such as decerebrated or decorticated posture, which are commonly associated to vegetative or minimally conscious state.

In severe brain injury the most significant clinical prognostic factors are represented by severity of coma (GCS), coma duration and post-traumatic amnesia.

Very severe brain injury with prolonged coma (coma duration of at least 15 days) other clinical features emerging during coma recovery may be of interest, such as spontaneous motor activity, psychomotor agitation, hypersexuality (Klùver-Bucy) and the time interval from brain injury to recovery of safe oral feeding.

Finally, PCS, as a measure of global disability, including the interval from brain injury to the administration of the scale and need of intensive nursing care, may be an interesting evaluation tool for predicting final outcome in patients with prolonged disturbances of consciousness.

If our preliminary results will be confirmed in larger studies, spontaneous motor activity and psychomotor agitation might be favourable prognostic features for recovery of consciousness in vegetative and minimally conscious state.

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Predicting one year clinical outcome in traumatic brain injury (TBI) at the beginning of rehabilitation

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Summary

Predicting long-term clinical outcome for patients with traumatic brain injury (TBI) at the beginning of rehabilitation provides essential information for counseling of the family and priority-setting for the limited resources in intensive rehabilitation. The objective of this study is to work out the probability of the one-year outcome at the beginning of rehabilitation. Sixty-eight patients with moderate-to-severe TBI and known one-year outcome were employed for outcome prediction using the logistic regression model. A large number of prospectively collected data at admission (age, Glasgow Coma Scale [GCS] Score, papillary response), during intensive care unit (ICU) management (duration of coma, intracranial pressure [ICP] and its progress) and at the beginning of rehabilitation (baseline Functional Independence Measure [FIM], Neuro-behavioral Cognitive Status Examination [NCSE] and Functional Movement Assessment [FMA]) were available for preliminary screening by univariate analysis. Six prognostic factors (age, GCS, duration of coma, baseline FIM, NCSC and FMA) were utilized for the final logistic regression model. Age, GCS and baseline FIM at the beginning of rehabilitation have been found to be independent predictors for one-year outcome. The accuracy of prediction for a good Glasgow Outcome Score is 68% and an outcome for disability (either moderate or severe) is 83%. Validation of this model using a new set of data is required.

Keywords: Head injury; prognosis; Glasgow Come Scale; Glasgow Outcome Scale; logistic regression model.

Introduction

Reliable prediction of outcome in the first few days of severe head injury has facilitated counseling of the family as well as appropriate allocation of resources of the intensive care unit (ICU). The accuracy of these outcome prediction programs in traumatic brain injury (TBI) has been proven to be good, in the region of 70–80% [1, 3–5], for the extremes such as mortality and favourable outcome, but poor in predicting severe disability (12.2%) [5]. Predicting good outcome at the beginning of rehabilitation [2, 6] has been assessed in the mid-1990s. Age, Glasgow Coma Scale (GCS) score and Disability Rating Scale are confirmed to be the three independent factors that contribute to its validation accuracy for predicting a good one-year outcome of 68% [6].

Intensive rehabilitation for TBI has been shown to improve early functional outcome (''return to work'') at 2 to 3 months but one-year clinical outcome was unchanged [8]. This cohort of sixty-eight patients had all the common prognostic factors at admission and ICU stay prospectively collected. Baseline and subsequent monthly FIM (Functional Independence Measure (FIM)), NCSE (Neuro-behavioural Cognitive Status Examination (NCSE)) and FMA (Functional Movement Assessment (FMA)) were also prospectively documented for a maximum of one year. It is therefore in this group of patients that accurate prediction of outcome will facilitate selection of patients for intensive rehabilitation.

Sequential Bayes method has been shown to be accurate in predicting TBI outcome in the Glasgow Head Injury Prediction Program [3, 5]. It has the advantage of allowing missing data, but the disadvantage of assuming that all prognostic factors are statistical independent. A logistic regression model [7] was selected for this study because we did not have missing data and also we now know that not all the factors we collect are statistical independent.

Materials and methods

This group of sixty-eight patients were recruited in the year 1997–9, where clinical data on admission, during the acute and rehabilita-

Table 1. *Accuracy of prediction by logistic regression at three time points: model A using admission data only; model B using both admission and acute management phase data; and model C, using admission, acute and rehabilitation data*

Variables	Model A (p-value)	Model B (p-value)	Model C (p-value)
Age	0.008	0.01	0.013
GCS	0.001	0.005	0.013
Coma duration	–	0.07	NS
Baseline FIM	–	–	0.008
Baseline NCSE	–	–	NS
Baseline FMA	–	–	NS
Outcome prediction (accuracy, %)			
Overall outcome (Apparent accuracy rate)	71	72	77
Moderate/Severe disability	69	69	83
Good recovery	72	75	69

NS Statistically not significant.

tion phases were prospectively collected. Moderate to severe head injuries were included. This was a head injury outcome study. Patients with severe spinal, pelvic or long bone fractures resulting in severe disability were excluded. Age, GCS, duration of coma, mechanism of injury, computerized tomography (CT) finding, ICU stay, number of days ICP-monitored, baseline FIM, NCSE and FMA were screened by univariate analysis for statistical significance. Based on this, six prognostic factors were therefore utilized for logistic regression analysis: age, GCS, duration of coma, baseline FIM, NCSE and FMA.

Results

This group of sixty-eight patients had a typical demographic and clinical characteristics for moderate-to-severe head injury: male predominant (80%), young age (mean age of 35 years) and a mean duration of coma of 14 days. When the six prognostic factors were assessed by the logistic regression model (Table 1), age, GCS and baseline FIM were proven to be the three independent factors predicting clinical outcome. There was only very moderate improvement in the performance of outcome prediction when more prognostic factors were utilized: from 71% to 77%. Adding baseline FIM data did not improve the performance of predicting good recovery, but it did to predicting moderate and severe disability (from 69% to 83%).

Discussions

Predicting clinical outcome in severe head injury using admission and acute management phase data has proven to be in the region of 70–80% [1, 3–5]. Adding baseline FIM data at the beginning of rehabilitation has not improved the performance of outcome prediction dramatically (Table 1), particularly predicting good recovery. However, the addition of baseline-FIM does improve the apparent accuracy of predicting one-year disability from 69% to 83%. This is the first prospective longitudinal study of moderate-to-severe TBI, where three independent prognostic factors (age, GCS and baseline-FIM) have been shown statistically to be contributing to outcome prediction. After its validation with a further sixty patients, the probability of a patient with TBI achieving a good recovery or moderate/severe disability at one year will be essential information for the counseling of family members and care providers for allocation of resources. Patients predicted to achieve good recovery require a short period of intensive rehabilitation, whereas patients predicted to remain disabled require a more lengthy (considerable) period of quality rehabilitation.

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Severe brain injuries in children

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Summary

Authors present a seven years retrospective study on 85 cases of severe brain injuries (SBI) in children (GCS </= 8) treated in the Pediatric and ICU Departments of the Clinic Hospital "Bagdasar-Arseni" Bucharest, Romania. The relationship between ICP, GCS on admission, the CT-scan/MRI alteration and the outcome evaluated by the Glasgow Outcome Scale (GOS) were studied in order to highlight the most important factors to improve prognosis. An overall mortality of 25.9% was found in this series. Authors concluded that the ICP values at admission >/= 20 mmHg, the Diffuse Axonal Injury (DAI) on MRI and the GCS on admission are factors of prognosis in SBI in children. The politrauma context is an aggravating factor for SBI in this age group. Other factors which influence GCS on admission may have prognostic importance i.e.: prehospital care, transport time and adequate transport conditions.

Keywords: Severe brain injury; children; ICP; GCS; DAI; outcome.

Introduction

Severe brain injuries (SBI) remain a major cause of mortality and morbidity in children. In the USA, children up to 15 years make up more than half of all new TBI cases with an annual incidence rate of 185 per 100.000 children [7]. After primary injury, surgical management aims to prevent secondary brain ischemia and herniation by compressive hematomas. However, debates continue about the best and necessary monitoring and medical treatment modalities, and therefore protocols might change over time [3].

Authors present a seven years retrospective study on SBI (GCS </= 8) in children (0–16 yrs) in order to analyze the outcome related to varied factors such as: ICP values, CT-scan alteration GCS at admission and associated lesions.

Material and method

The data of 85 children (0–16 yrs) with SBI treated in the ICU and Neurosurgical Pediatric Departments of the Bagdasar-Arseni Hospital from 1997 to 2003 were analyzed retrospectively. The SBI was defined as GCS at admission </= 8. The sex distribution was: 58 boys (68.2%) and 27 girls (31.8%). The age distribution was: 0–1 year: 6 cases (7.1%), 1–3 years: 10 cases (11.7%), 4–7 years: 27 cases (31.7%), 8–12 years: 31 cases (36.5%), and 13–16 years: 11 cases (13%).

The mechanisms of injury were: 54 car accidents (63.5%), 23 falls (27.1%), 3 domestic accidents (3.5%), 2 sport traumas (2.4%), 3 child abuse (3.5%). From all of these, 46 cases (54.12%) were in a context of politrauma. The multiple trauma cases included association of 2 lesions in 33 cases and 3 lesions in 13 cases. The associated orthopedic lesions were found in 15/46 cases, the abdominal lesions in 13/46 cases, thoracic lesions in 11/46 cases, spine lesions in 10/46 cases and ENT lesions in 10/46 cases. GCS at admission was 3 in 10 cases (11.8%), GCS 4 in 7 cases (8.2%), GCS 5 in 18 cases (21.2%), GCS 6 in 13 cases (15.3%), GCS 7 in 17 cases (20%) and GCS 8 in 20 cases (23.5%).

All cases underwent CT-scan of the brain within 6 hours of injury. The CT-scan (completed with MRI when necessary) on admission showed hematomas in 19/85 cases (22.4%), hemhorragic contusion/SAH in 23/85 cases (27.1%), hypodense/ischemia/edema lesion in 18/85 cases (21.2%) and DAI in 25/85 cases (29.3%). 19/85 cases (22.3%) were submitted to neurosurgical interventions in emergency.

The ICP monitoring was performed in all cases using Codman device with intraparenchymal or intraventricular catheter. The normal value of ICP was considered to be 15 mmHg in children and 8–10 mmHg in infants.

The outcome was evaluated by GOS at 6 months after injury. The mean period of follow-up was 3.7 years.

Results

13/46 cases (28.3%) of SBI in context of politrauma died. The overall mortality was 25.9% (22/85 cases). The outcome at six months was:

Table 1. *GOS related to the CT-scan/MRI alteration*

	GOS 1	GOS 2	GOS 3	GOS 4	GOS 5
Operated hematoma	1	–	1	4	13
Hypodense, edema	5	1	5	3	4
contusion, SAH	1	–	3	7	12
DAI	15	–	8	2	–

Table 2. *GOS related to the GCS on admission*

	GOS 1	GOS 2	GOS 3	GOS 4	GOS 5
GCS 3	10				
GCS 4	6	1			
GCS 5	3		9	6	
GCS 6	1		5	7	
GCS 7	2		2	1	12
GCS 8			1	3	16

GOS = 1 (died) in 22 cases (25.9%), GOS = 2 (vegetative state) in 1 case (1.2%),
GOS = 3 (severely disabled) in 17 cases (20%), GOS = 4 (moderately disabled) in 16 cases (18.8%) and GOS = 5 (good recovery) in 29 cases (34.1%).

The ICP > 20 mmHg was measured in 18 cases (21.2%) and ICP < 20 mmHg in 67 cases (78.8%). The GOS of children with **ICP < 20 mmHg** was: GOS = 5 in 12/18 cases (66.6%) and GOS = 4/18 in 6 cases (33.4%). The GOS of children with **ICP > 20 mmHg** was: GOS = 1 in 22/67 cases (32.8%), GOS = 2 in 1/67 case (1.5%), GOS = 3 in 15/67 cases (22.4%), GOS = 4 in 7/67 cases (10.45%) and GOS = 5 in 16/67 cases (23.9%). The 6 infants presents 5 cases GOS 3 & 4 and 1 case GOS 1. This is probably due to the immature brain which reacts inadequate to the injuries.

The GOS related to the CT-scan/MRI alteration are presented in Table 1:

- Operated cases group (19/85): GOS = 1 in 1 case, GOS = 3 in 1 case, GOS = 4 in 4 cases and GOS = 5 in 13 cases.
- For the group of non-operated haemhorragic contusion/SAH (23/85 cases), the GOS = 1 in one case, GOS = 3 in 3 cases, GOS = 4 in 7 cases and GOS = 5 in 12 cases.
- The group of hypodense/ischemia/edema lesion (18/85 cases) the GOS were: GOS = 1 in 5 cases, GOS = 2 in 1 case, GOS = 3 in 5 cases, GOS = 4 in 3 cases, GOS = 5 in 4 cases.
- The group of DAI (25/85 cases) showed the following GOS: GOS = 1 in 15 cases, GOS = 3 in 8 cases, GOS = 4 in 2 cases

The GOS related to the GCS on admission are presented in Table 2:

The posttraumatic seizures after 6 months was found in 3/63 cases (4.8%).

Discussions

SBI represents an important cause of mortality and morbidity in childhood. In the literature there are studies which correlate the GOS with GCS, metabolic, hematological, radiological and clinical profiles [9, 18]. Other studies correlate the hyperglycemia at admission and the prognosis in children with SBI [4]. In this study authors analyzed the correlation between GCS at admission, ICP values, CT/MRI alteration and the outcome in children 0–16 year old affected by SBI.

Intracranial pressure monitoring (ICP) is appropriate in infants and children with SBI (GCS score </= 8) and abnormal admission CT scan. SBI is defined as a GCS score of 3–8 after cardiopulmonary resuscitation. An abnormal CT scan demonstrates hematoma, contusions, cerebral edema, and/or compressed basal cisterns. In our series, the MRI was performed to diagnose DAI.

SBI patients are at high risk for intracranial hypertension [10, 14]. The combination of SBI and an abnormal head CT scan suggests a high likelihood (53–63%) of raised ICP [15]. However, even with a normal admission CT scan, intracranial hypertension may be present [11, 16].

Michaud *et al.* [13] found that 94% of children with ICP max < 20 mm Hg survived, whereas only 59% with ICP max > 20 mm Hg survived. Forty eight % of children with ICP elevation > 1 hr survived, compared with 89% of children with ICP elevated for <1 hr. Outcome was also better in children with ICP elevation for <1 hr [13].

Downard *et al.* [5] in a stepwise logistic regression analysis, ICP > 20 mm Hg, was significantly associated with an increased risk of death [5].

Esparza *et al.* [6] performed a retrospective review of 56 pediatric patients with SBI. They used a treatment threshold of ICP > 20 mm Hg. Surgical evacuation of mass lesions was performed as needed, but no decompression craniotomy was done. They found that the

group of patients with ICP > 20–40 mm Hg had a mortality rate of 28%, whereas the group with an ICP > 40 mm Hg had a mortality rate of 100% [6].

In our study no mortality was registered in the group of ICP < 20 mmHg, all the 22/67 cases (32.8%) which died had the ICP > 20 mmHg. The infants group presents poor prognosis in comparison with children because of the immature brain.

Pigula *et al.* [17] analyzed the influence of hypoxia and hypotension on mortality from SBI in two prospectively collected pediatric (age </= 16 yrs) databases. Hypoxia was defined at admission in emergency department as PaO2 </= 60 mm Hg. Authors concluded that hypotension is the most influential secondary insult determining short-term mortality rate [17]. Hypotension with or without hypoxia was associated with mortality rates approaching those found in adults.

Carter *et al.* [2] in a recent study reported the outcome at 5 years in children with SBI and found 46 (43.8%) children with a good outcome, 10 (9.5%) moderately disabled, 2 (1.9%) severely disabled, 3 (2.9%) vegetative and 44 (41.9%) died.

In our series the overall GOS at 6 months was GOS = 1 in 22 cases (25.9%), GOS = 2 in 1 case (1.2%), GOS = 3 in 17 cases (20%), GOS = 4 in 16 cases (18.8%) and GOS = 5 in 29 cases (34.1%).

High mortality in combined cranio-abdominal trauma is caused by the injury severity, the traumatic shock and mutual burden syndrome presence [8]. In our series the SBI without politrauma represents 39 cases (46%) and SBI with politrauma 46 cases (54%). The overall mortality (22 cases – 25.9%) was constituted by 13 cases of politrauma and 9 cases without politrauma, which suggests that the context of politrauma represents an aggravating factor of prognosis.

The relationship between GCS at admission and GOS is debated in the literature.

Sawauchi *et al.* [19] analyzed the records of 779 patients with head injury who had an admission GCS of 9 or more and found that 7% developed progressive brain injury as evidenced on serial CT scans [19]. In the actual series authors studied the relationship between GCS at admission and GOS at 6 months and found a correlation between the two parameters, children with GCS 7 and 8 (28 cases GOS = 5) had the best prognosis and the high mortality rate was found in children with GCS 3 and 4 (16 cases GOS = 1).

Computed tomography – CT is a rapid and easily performed investigation, also in monitored patients. It is the most relevant imaging procedure for evaluation of surgical lesions. CT is a suitable method to follow the dynamics of lesion development giving an insight into the corresponding pathological development of the brain injury. Magnetic resonance imaging – MRI is more sensitive for all posttraumatic lesions except skull fractures and subarachnoid hemorrhage. The scanning time is long, and there is an ever present problem with the monitoring of patients outside the MRI field. If CT does not demonstrate pathology as can adequately be explained to account for clinical state, MRI is warranted. Follow-up is better with MRI as it is more sensitive to parenchymal changes [1].

Sawauchi *et al.* [19] studied the appearance of progressive brain injury associated with patient age, admission GCS, injury mechanisms, skull fracture and hemorrhagic lesions on the initial CT scan. Patients with the extracerebral lesions deteriorated 4 hours after injury, whereas those with intracerebral lesions deteriorated 8 hours after injury. The outcome based on GCS was significantly associated with age, type of intracranial lesion, GCS following deterioration, the mechanism of injury and surgical treatment. It is concluded that early repeated CT scan is indicated in patients with risk factors of developing progressive brain injury [19].

In this series we found a great mortality rate (GOS = 1) in children with DAI (15/85 cases – 17.65%) while the best prognosis (GOS = 5) was found in cases with surgically evacuated lesions (13/85 cases – 15.3%) and contusion, SAH (12/85 cases – 11.1%).

The degrees of hydrocephalus and of hypoperfusion in the temporal lobes are significant risk factors for late post traumatic epilepsy – PTE. Another main finding of our study is the absence of epileptic influence on cognitive disorders [12]. A significant association of early post-traumatic seizures with an unfavorable outcome was observed. Early post-traumatic seizures appear to be an acute reaction of the brain to cortical damage with little independent impact on the management of head injury [20]. In our series the PTE represents 3/63 cases (4.8%).

Conclusions

SBI in children have poor prognosis with high mortality and morbidity rate. Factors of poor prognosis in our series are: low level of GCS on admission, DAI on the CT-scan and ICP value > 20 mmHg. Factors

which influence GCS on admission and may have prognostic importance are: the pre-hospital care, the transport time and the adequate transport conditions. Patients with associated lesions had poor prognosis, longer period of hospitalization and more difficult recovery. Authors plead for improvement of the pre-hospital care and the patients monitoring during the hospitalization in order to improve prognosis in SBI.

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The locked-in syndrome: a challenge for therapy

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Summary

The locked-in syndrome (LIS) is a severe condition originated by a ventral pons lesion causing quadriplegia and anarthria but with a preserved consciousness. LIS seems to be a well defined clinical picture, although different problems still persist, such as the diagnosis as it is usually mistaken for akinetic mutism and a vegetative state; the unclear prognosis, because of the patient's psychological state and the lack of information and data concerning the different types of available treatment and the need for results. Rehabilitation is a challenge for physicians, new methods and techniques of specialized treatments for these patients are opening a new future that will allow us to abandon the initial pessimism. A more efficient rehabilitation of these patients depends on the intensity of the rehabilitation, the multidisciplinary approach, and duration of the treatment.

Keywords: Locked-in-syndrome; akinetic mutism; vegetative state.

Introduction

The locked-in syndrome (LIS) is a severe condition originated by a ventral pons lesion consisting of quadriplegia and anarthria with preserved consciousness. This syndrome is also known as Ventral Pontine Syndrome, state of Supranuclear Motor De-efferentation, and False Coma by Cerebro-medullary Spinal Disconnection. The syndrome has recently begun to capture the interest of professionals working in the area of acquired brain injury due to the fact that these patients survive for a longer period of time and also due to the families and doctors inquiring for specialized attention for these patients [6]. Today, these patients constitute a professional challenge for the medical personnel that must attend them, they constitute a group of patients that were considered to have a rare disease but now beginning to be "more visible" due to the technical advances that allow a higher rate of survival of these patients and more precise diagnosis. Now a days the French association for Locked-in-syndrome (ALIS) has 283 associates with a range of age from 10 to 84 years; most of them had the onset of LIS between the age of 25 and 60 years, with a peak in the fourth decade.

Anatomical and clinical features

The locked-in syndrome is a consequence of a brainstem lesion (ventral pons lesion) with the implication of the cortico-spinal tract which produces acute quadriplegia and anarthria with preserved consciousness. This pontine lesion affects long pathways running through the brainstem as well as cranial nerves III and XII (interruption of the cortico-bulbar tract). Most patients with LIS suffer from de-cerebrate posturing, the rigid extension of both the upper and lower limbs. In addition, patients with LIS present respiratory problems, associated with breathing insufficiency. The lesion(s) to the low cranial nerves can produce a facial, tongue and pharyngeal diplegia with anarthria, causing severe difficulties in swallowing and dysphonia. While awake, patients have lateral gaze palsy and paralytic mutism, they can open their eyes, blink and make voluntary conjugated vertical movements of the eyeballs. These vertical eye movements are the only way of communication.

Differential diagnosis of locked-in syndrome

LIS seems to be well defined, although different problems persist when confronting the syndrome in both acute and sub-acute stages. First problem is a

diagnosis, usually confused with akinetic mutism, and vegetative state. The second problem is the information and prognosis. The third problem is the diagnosis of the patient's psychological state. Finally, the fourth problem is the lack of information and data concerning the different types of treatment that are available and their results. In our survey we found that the correct diagnosis was usually made around the middle of the second month after the onset of LIS (mean of 78.76 days). A differential diagnosis between vegetative and minimally conscious states has to be made. To diagnose minimally conscious states (MCS) one or more of the following clinical features should be present: following simple commands, manipulation of objects, gestural or verbal 'yes/no' responses, intelligible verbalization, stereotypical movements (blinking, smiling) that occur in a meaningful relationship to the eliciting stimulus. These responses must occur on a sustained basis before the diagnosis of MCS can be made [3]. Patients diagnosed with MCS on admission to rehabilitation had significantly more favorable outcome across the first year post-injury, relative to patients diagnosed with vegetative state [3]. Once agreed that diagnostic tools should play an important part in a diagnosis, the role of bedside examination in diagnosing LIS cannot be discounted, since it has been demonstrated that it is normally a family member who first discovers that a patient with LIS is aware of surrounding.

Although initial computerized tomography (CT) can infrequently be unrevealing, serial and follow-up CT scanning have proven their usefulness in the majority of cases as a prognostic tool of the basilar artery (BA) syndrome. This conclusion is based on a study of 22 patients with ischemic stroke, as a single event, in the territory of BA using CT and clinical-radiological features [6]. The authors found that the basilar artery syndrome may be divided into five subtypes: Type 1. Incompatible with life, the complete type. Type 2. Extensive brainstem infarct that may result in LIS. Type 3. Infarctions in part of the BA territory. Type 4. Characterized by a top of the BA syndrome Type 5. Negative CT BA syndrome.

Consciousness, cognition and emotions in patients with LIS

In the past it was assumed that patients suffering from LIS have consciousness preserved, but preserved consciousness does not mean they are cognitionally fully aware. We cannot say that cognition is completely intact. In our study we found that neuropsychologically, 86% of patients with LIS had a good attentive level, 97.6% were temporally oriented, 76.7% could read, 18.6% reported memory problems, and 24% showed visual deficit (found mainly in patients with LIS originated by Traumatic Brain Injury (TBI)). 47.5% of patients reported a good mood state and 12.5% reported feeling depressed. 61.1% of patients reported having sexual desire, but only 30% maintained sexual relations. 78% of the patients were capable of emitting sounds and 65.8% could communicate without technical aid. 73.2% of the patients enjoyed going out, and 81% met with friends at least twice a month. Only 14.3% participated in social activities and 23.8% watched television regularly. Finally, nearly 100% of the patients reported being sensitive to touch to any part of their bodies.

These data suggest that patients have consciousness preserved, and probably they are mostly aware of what is happening around them. However, it is our view that their cognitive appraisal of what is happening, interoceptively and exteroceptively, is in fact affected by his/her mood and emotional state which are altered in the majority. The possibility of these patients to have neuropsychological impairments, specifically due to the ventral pons lesion, have to be determined. The reported cognitive deficits depend on anatomical site of the lesion and disrupted connections with the rest (one or more) cognitive functional network(s). However, different are those patients who sustained traumatic brain injury and the lesion in the ventral pons, and also in other parts of the brain outside the basilar artery territory. These patients will have affected cognition depending on where the areas of the brain lesions are localized and in what way are these lesions related to remaining cognitive and behavioral functions. Patients suffering from LIS will require always neuropsychological treatment as part of their holistic approach which can be provided by a multidisciplinary team.

What treatment approach?

The outcome of a treatment will be always good or bad depending on the final goal established on admission of the patient. Some authors and organizations consider the prognosis of LIS as very poor. This view was maintained by many a physician in the second part of the last century, before new technological facilities

and renewed interest arose for these patients. In our survey the principal treatments, when present, were the pharmacological approach and physiotherapy. However, 47.1% of the patients were not receiving treatment of any kind at the time of the survey. At the present time we can say that important improvement for the patient and the family is possible to achieve if rehabilitation is given with the appropriate length of time, with technical aid and well trained professional team.

To what point is the rehabilitation possible and reasonable is something we still have to solve but new attempts in the field of research are very promising. Interesting are the studies carried out by The Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Germany. They have found that a muscle-independent communication channel through a brain-computer interface, direct connection between brain and computer, will overcome this problem of patients with LIS. They contrasted the number of technically elaborated brain-computer interfaces with the number of systems used in the daily life of locked-in patients and concluded that a profound knowledge and consideration of psychological principles are necessary to make brain-computer interfaces feasible for locked-in patients [4]. With the necessary duration of treatment, timing and interdisciplinary team in therapy Pickl [5] describes how patients with LIS can progress from the so-called classical to the incomplete locked-in state. He describes outcomes also according to the impact of a patient's personality on the course and goals of the treatment as well as on the mode of communication. Cairns and Stein described a motor function improvement following intrathecal baclofen pump placement in a patient suffering from LIS [1]. The patient had minimal volitional motor function and severe spasticity in all four extremities and showed a significant improvement in volitional motor function following intrathecal baclofen pump therapy to control spasticity. They suggest that intrathecal baclofen pump therapy may improve motor function in selected patients with LIS. Hopeful is the work reported by Casanova, Lazzari, Lotta, Mazzucchi [2] showing the prognosis and the recovery of patients with LIS who received an early and subsequently late intensive rehabilitation in a form of a consecutive sample program and were followed-up for 5 months to 6 years in three different rehabilitation centers in Italy. They studied 14 patients with LIS who underwent the same treatment: intensive nursing care and intensive and early rehabilitative program, including physiotherapy and respiratory, swallowing, and speech training. Four patients received occupational therapy. Four patients had also oculomotor training. After discharge every patient continued with a rehabilitative maintenance care. They found a significant motor recovery in 21% of subjects, within 3 to 6 months from the onset of the morbid event; a complete swallow recovery in 42%; verbal communication in 28%; communication through devices in 42%; effective bladder and bowel control in 35%; and good breathing patterns in 50%. The follow-up revealed the mortality rate of 14% and only 2 complications were reported. They concluded that intensive and early rehabilitation, beginning within 1 month after the morbid event, improved the functional recovery and reduced the mortality rate, as reported in the literature, to 60% about 10 years ago.

In conclusion, rehabilitation and treatment for patients suffering from LIS is worthwhile and promising. The optimal improvement can be expected when allowances for treatment are made with regards to length of time, intensity, multidisciplinary approach, technical advances, and a well trained team that is willing to fight for the recovery of the patients, believing that all the efforts are possible and worthwhile. The prognosis of patients with LIS maybe then directly related to the long-term treatment and to the family's ability to access and make use of medical and paramedical resources.

Acknowledgements

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E. Addendum

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WFNS committee for neurorehabilitation

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From the beginning of neurological surgery on, the preservation and restoration of impaired brain and spinal-cord functions as an original task for neurosurgeons demand their involvement with issues of functional neurorehabilitation including neurosurgical re-engineering of the damaged brain and spinal cord. Many years of own experience and the first international Congress of Early Rehabilitation that took place in 1990 at the start of the "Decade of the Brain" were the occasion for the proposal to found an *ad hoc* committee for functional neurorehabilitation in neurosurgery of the World Federation of Neurosurgical Societies (WFNS).

Formed in 1997, the WFNS committee supports all efforts regarding personal and regional activities, teaching, research, recommendations, guidelines, and practical application to improve neurosurgical quality management within the spectrum of holistic neurorehabilitation around the world. It was in Copenhagen in Denmark at the 11th EANS when delegates met officially for the first time at the University Clinic of Neurosurgery, Rigshospitalet, September 21st, after Dr. Flemming Gjerris, the Congress President, took up our proposal and for the very first time adopted the issue of neurosurgical neurorehabilitation as an equal-priority topic at all into the scientific agenda of the congress of an international neurosurgery society. This was followed by the 11th AANS Congress that took place in Lahore in 1999; the 12th WFNS, in Sydney in 2001, and the planning of the 13th WFNS that shall be held in Marrakech in 2005; the 4th PAN ARAB Neurosurgical Congress in Cairo in 2002, and the 5th PAN ARAB Congress in Amman, Jordan, in 2004; the 24th Congresso Brasileiro De Neurochirurgia, Fortaleza Brasil, in 2002; the 4th Asian Conference of Neurological Neurosurgeons (ACNS) in Hong Kong in 2002; and the 5th Conference at Karawasi Tangerang, Indonesia, in 2004; the 9th Pan Arab Union of Neurological Societies, which was held at Cairo and Sharm Sheikh, Egypt, in 2003; the 3rd Chinese Congress of Neurotraumatology, in Tianjing, China, in 2004; and the 11th ASEAN Congress of Neurological Surgeons, in Bali, Indonesia, in 2004.

Along with the scientific progress in biotechnology and functional neuroimaging (MRI, PET, transcranial magnetic stimulation), neurosurgeons have become increasingly interested and actively involved in rehabilitation science (Fig. 1). Some have developed specially designed institutions for early (acute) and subacute neurorehabilitation. Attached to the acute services, neurosurgeons thus become responsible for neurorehabilitation and are able to manage all kinds of complications, which have significantly improved the early and late functional outcome.

WFNS neurorehabilitation committee, November 2004

Coordinator WFNS Committees: Senator Jacques BROTCHI, Belgium, WFNS President-elect (Fig. 2)
Founding and Honorary Chairman: Klaus R. H. von WILD, Germany
Chairman: Yoichi KATAYAMA, Japan (Fig. 3)
Secretary: Wai S. POON, Hong Kong, China (Figs. 1, 2)
Historian: Matej Lipovšek, Slovenia

Committee members

Afghan Society of Neurosurgery (Affiliate): Ahmad Fawad PIRZAD
Albanian Society of Neurosurgery (Affiliate): Lambi LEKA

Fig. 1. 3rd conference of the WFNS Committee for Neurorehabilitation in conjunction with the 1st conference of the World Academy for Multidisciplinary Neurotraumatology (AMN), Brescia, Italy, March 29th, 2004. WFNS members and guests on occasion of the Founding and Honorary Chairman's Dinner (from left to right): Joachim Liepert, Germany, Wai Song Poon, Hong Kong China, Mohammed Al Joharji, Kingdom of Saudi Arabia, Marcos Tatagiba, Germany, Rüdiger J Seitz, Germany, Takaomi Taira, Japan, Rita Formisano, Italy, Hubert R Dinse, Germany, Takamitsu Yamamoto, Japan, Tadej Strojnik, Slovenia, Stephani Ng, Hong Kong China, David W Mulholland, USA

Fig. 2. Senator Jacques Brotchi, Brussels, attending the 3rd WFNS Conference in Brescia. Front left Wai S. Poon, Hong Kong

Fig. 3. Y. Katayama, Tokyo, Congress President 2nd WFNS Conference, together with T. Kawase, Tokyo (right), and K. von Wild, Münster on occasion of the 2nd WFNS Conference in Tokyo, July 11th, 2002

South Africa Society of Neurosurgery: Freddie KIECK
Asian Australasian Congress of Neurosurgeons (Affiliate): Tetsuo KANNO, Japan
Ali RAJA, Pakistan
Austrian Society for Neurosurgery: Gudrun SEIWALD
Brazilian Academy of Neurosurgery: Hildo Azevedo FILHO
Brazilian Society of Neurosurgery: Marcos MASINI
Society of British Neurological Surgeons: B. M. SONI
Central European Neurosurgical Society: Juraj STENO, Slovakia
Chilean Society of Neurosurgery: Wolfgang MAUERSBERGER
Chinese Neurosurgical Association: Chun-Jiang YU
Croatian Neurosurgical Society: Miroslav VUKIC
Czech Neurosurgical Society: Jaroslav PLAS
Danish Neurosurgical Society: Ole OSGAARD
Egyptian Society of Neurological Neurosurgeons: Adel EISA, Abdel Wahab IBRAHIM, Ahmed ISSA
French Society of Neurosurgery: Philippe DECQ
German Neurosurgical Society: Thomas ROMMEL
Hellenic Neurosurgical Society: George FOROGLOU
Hong Kong Neurosurgical Society: Fan YW, Wai S. POON
Neurological Society of India: K.V.A. SHASTRI
Indonesian Neurosurgical Society: Kahdar WIRIADISASTRA
Israel Neurosurgical Society: Nissim RAZON
Italian Society of Neurosurgery: Alessandro DUCATI, Paolo ZAMPIERI
Japanese Neurosurgical Society: Takeshi KAWASE
Japanese Congress of Neurological Surgeons: Yoichi KATAYAMA
Jordanian Neuroscience Sociey: N.J.S. KHOURY
Korean Neurosurgical Society: Hun Joo KIM
Latin American Federation of Neurosurgical Society: Hector GIOCOLI
Latvian Association of Neurosurgeons: Janis OZOLINSH, Anita VETRA
Lithuanian Society for Neurosurgery: Rimantas VILCINIS
Macedonian Society of Neurosurgery: Vladimir MIRCEVSKI
Neurosurgical Association of Malaysia: Jafri Malin ABDULLAH
Moroccan Society of Neurosurgery: A. El KHAMLICHI
(President, WFNS World Congress of Neurosurgery 2005, Marrakech, Morocco 2005)
The Netherlands Society of Neurosurgeons: Hans VAN DER AA
Nigerian Society of Neurological Sciences (Neurosurgical Section): Tayo SHOKUNBI
Pakistan Society of Neurosurgeons: Rashid JOOMA
Pan African Association of Neurologiocal Sciences (Neurosurgical Section): Kazadi KALUNGA, Kongo
Pan Arab Neurosurgical Society: Ahmad AMMAR, Mohamed Al JOHARJI, Saudi Arabia
Academy of Filipino Neurosurgeons (Affiliate): Gerado D. LEGASPI
Polish Society of Neurosurgery: Jan HAFTEK
Portuguese Neurosurgical Society: Carlos FERRO
Romania Society for Neurosurgery: Alexander V. CIUREA
Association of Neurosurgeons of Russia: Alexander A. POTAPOV
Scandinavian Neurosurgical Society: Trygge LUNDAR, Ingunn RISE, Norway
Neurosurgical Association of Serbia and Montenegro: Vladimir JOVANOVIC, Serbia
Slovenian Neurosurgical Society: Tadej STROJNIK
South Cone Society of Neurological Surgeons: Eduardo A. KAROL Argentina
Swiss Society of Neurosurgery: R. HEILBRONNER
Taiwan Neurosurgical Society: Alexander Dah-Jium WANG, Chiu Wen-TA
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Academia Multidisciplinaria Neurotraumatologica AMN*

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Objective

The Academia Multidisciplinaria Neurotraumatologica or World Academy for Multidisciplinary Neurotraumatology, abbreviation AMN*, was established in Munich on May 19th, 2003 (Fig. 1a), in following the suggestions of Dr. Tetsuo Kanno, Professor for Neurosurgery, President and Director of Fujita Health University, Toyoake, Aichi, Japan. As Honorary Member of the European Academy for Multidisciplinary Neurotraumatology, EMN (Fig. 1b), he gained his experience of the close, interdisciplinary-transdisciplinary cooperation of neurosurgeons with neuroscientists and therapists as well as with politicians, care providers and care givers in the challenging special field of Neurotraumatology beyond the geographic, cultural and socio-economic boarders in Europe. Our key aim was and will be to promote prehospital, acute medical, clinical care, rehabilitation and science in all aspects of Neurotraumatology all

a b

Fig. 1. AMN founding members. (a) AMN Founding Members after signing the constitution of the AMN, München, May 19th, 2003. From left to right: Wai S. Poon, Anwar El Etribi, Tetsuo Kanno, Monika von Wild, Giorgio A Brunelli, Klaus von Wild, Marion Prosiegel and his wife Eva, Motoi Shoda and his colleague Shigehiko Kuno. (b) Tetsuo Kanno, the initiator of the Academia Multidisciplinaria Neurotraumatologica, Honorary Member of the Euroacademia Multidisciplinaria Neurotraumatologica at the 8th EMN in Graz, Austria, together with Klaus von Wild, President EMN, May 21, 2003

* The AMN is involved directly and exclusively in non-profit activities in the sense of "activities entitled to taxation relief" in the taxation classification.

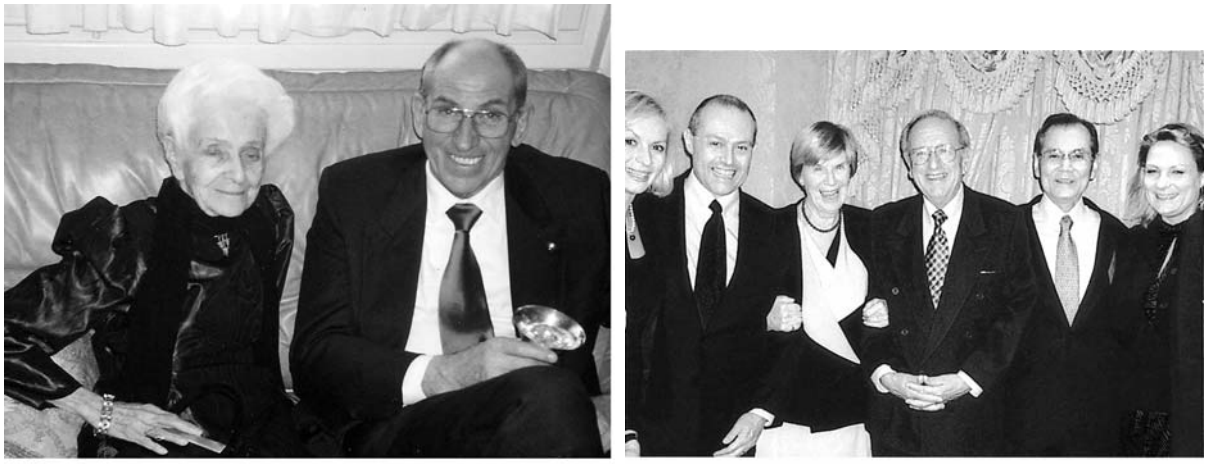

Fig. 2. AMN founding members. (a) Giorgio A Brunelli and Professa Rita LEVI-MONTALCINI, Rome, Nobel Prize Laureate in Medicine 1986, for her discoveries of growth factors, Guest of Honour of the of the 5th Symposium on Experimental Spinal Cord Repair and Regeneration, Brescia, March 28, 2004. (b) President George P. Prigatano, USA, Congress President 2nd World AMN congress (second left) and his wife Dagmar (left and to the right side) Ann-Lise Christensen, Denmark, Vice President with the Academicians Joaquin Fuster, USA, Tomio Ohta, Japan, and Nicole von Steinbüchel, Switzerland, at the Presidential dinner on occasion of the 2nd World AMN Congress in Phoenix, Arizona, November 12, 2004

over the world, regardless the present sate of the social health care, political, and economic systems. Head and spinal cord injuries can happen to everybody, everywhere and every time. Neurotrauma prevention and the victim's social reintegration mark the beginning and the final target of the ongoing chain of our multidisciplinary efforts to finally improve health related quality of life after brain and spinal cord injury in the world.

Purpose

Therefore, the purpose of the World AMN is the advancement of neurotraumatology in research, practical application and teaching. This purpose is to be attained by, in particular:

1. The organisation of international congresses as well as participation in such events including regional and national workshops and educational meetings in all fields of neurotraumatology. Annual AMN meetings have a main theme and draw on areas of expertise in the locale in which the meeting will be held. Each meeting is meant to provide for poster sessions and encourage dialogue between senior and junior colleagues, as well as across disciplines.
2. Commitment to excellence in education through organisation of workshops and intensification of cooperation with scientific academies, societies, associations as well as research institutions and companies who are concerned with questions related to neurotraumatology.
3. The communication between national and international academies, societies and associations concerned with neurotraumatology in research, practical applications and education.

Annual World AMN congresses

1st World AMN Brescia, Italy, March 29–30, 2004

Congress President Professor Giorgio A. Brunelli, M.D., Ph.D., Emeritus Professor of Orthopaedics, Trauma and Handsurgeon, Foundation for Research on Spinal Cord Lesions

Main theme: Re-engineering of brain and spinal cord lesions (Fig. 2a)

2nd World AMN Phoenix, Arizona, USA, November 11–13, 2004

Congress President George P. Prigatano, Ph.D., Professor of Neuropsychology, Newsome Chair, Department of Clinical Neuropsychology, Barrow Neurological Institute, Phoenix, Arizona, USA

Main theme: neuropsychological and neurosurgical collaboration in the treatment of TBI patients (Fig. 2b)

Fig. 3. AMN founding members. Anne-Lise Christensen (right), EMN Honorary Member and Lucia Willadino Braga after signing the AMN constitution in Graz, Austria, on occasion of the 8th EMN, May 21, 2003

3rd World AMN Nagoya, Japan, March 9–10, 2005

Congress President Tetsuo Kanno M.D., Ph.D., Professor of Neurosurgery, President and Director of Fujita Health University, Kutsukake-cho, Toyoake Aichi, Japan

Main theme: What and how is the Multidisciplinary Approach to Neurotrauma? Prevention, resuscitation, intensive care and emergency operative treatment, early rehabilitation, social reintegration, and quality of life following brain and spinal cord lesions.

In conjunction with Special Session of the WFNS Neurorehabilitation Committee on functional deep brain, motor cortex, and spinal cord stimulation, and cell transplantation

4th AMN Copenhagen, Denmark, May 17–19, 2006

Congress President Anne-Lise Christensen, Ph.D. Professor of Neuropsychology Center for Brain Injury Rehabilitation at the University of Copenhagen

Main theme: Holistic approaches to neuropsychological rehabilitation after TBI (Fig. 3)

5th AMN Düsseldorf, Germany, May, 2007

Congress President Volker Hömberg, M.D., Ph.D., Professor of Neurology, St Mauritius Therapieklinik Meerbusch, Neurologisches Therapiecentrum Köln, Neurologisches Therapiecentrum an der Heinrich Heine Universität Düsseldorf

Main theme: Functional neuroimaging techniques in posttraumatic rehabilitation. Understanding motor recovery and how this information can be transferred to understanding other forms of recovery following TBI

6th AMN Brasilia, Brazil, 2008

Congress President Lucia Willadino Braga, Ph.D., Professor of Neuropsychology da Rede SARAH de Hospitais, Brasilia-Rio de Janeiro, Brazil

Main theme: Recovery and rehabilitation of children after TBI and SCI (Fig. 3)

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The academy for multidisciplinary neurotraumatology on internet

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NBIRTT, the National Brain Injury Research, Treatment and Training Foundation

G. A. Zitnay

The National Brain Injury Research, Treatment and Training Foundation was founded by me to support new cutting edge research to find a "cure" for brain injury and to support programs and projects that significantly improve the quality of life for persons with brain injury.

NBIRTT has also funded the development of evidence based medical guidelines in brain injury, training seminars and the development of the QOLIBRI, a novel assessment instrument for measuring health related Quality of Life after Brain Injury.

Currently, the Board of Directors of NBIRTT is organizing an international scientific meeting to evaluate the progress in research in brain injury over the last decade and to develop a new future thinking research agenda for the next decade with the goal of creating a consensus statement on needed research. The international meeting will be held in Johnstown, Pennsylvania, October of 2005.

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SpringerNeurosurgery

Alberto Alexandre, Albino Bricolo,
Hanno Millesi (eds.)

Advanced Peripheral Nerve Surgery and Minimal Invasive Spinal Surgery

2005. XI, 157 pages.
Hardcover **EUR 98,–**
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ISBN 3-211-23368-7
Acta Neurochirurgica, Supplement 92

The papers in this volume summarize information about the most recent and effective techniques for treating diffcult functional problems and painful situations by using minimally invasive spinal surgery techniques. Spinal endoscopy both for diagnostic and treatment purposes is presented as well as microsurgical operations for spinal problems, intradiscal techniques for the treatment of disc degenerative pathology, and dynamic stabilization techniques together with an up-to-date review of physiopathology of the diseases. New trends in peripheral nerve surgery are presented. Also the problem of traumatic nerve lesions in different anatomical districts is analyzed with special attention on the theme of thoracic outlet syndrome. The posttraumatic aspects of this disease are discussed both in respect of its causative mechanisms, and its medicolegal aspects.

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SpringerNeurosurgery

Berndt Wowra, Jörg-Christian Tonn,
Alexander Muacevic (eds.)

Gamma Knife Radiosurgery

European Standards and Perspectives

2005. VII, 111 pages. With partly coloured figures.
Hardcover **EUR 89,–**
Reduced price for subscribers to "Acta Neurochirurgica": **EUR 80,–**
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ISBN 3-211-22870-5
Acta Neurochirurgica, Supplement 91

Gamma knife radiosurgery has grown continually in importance in recent years. However, there was a lack of established clinical and physical quality standards and a good knowledge of the possibilities of radiosurgical treatment for brain lesions. This book fills the gap by giving an overview of the current status of European gamma knife radiosurgery. Leading european experts report on their specialities in this field which is a state-of-the-art summary of the possibilities and results of their current work. The book encompasses all important as well as the more rare indications. All relevant technical and clinical quality standards are addressed. Tailored planning strategies are described for different indications. All professionals who care for patients with neurosurgical disease, such as neurosurgeons, radiosurgeons, radiologists, radiation oncologists and neurologists will find the book highly useful for the management of patients with benign and malignant brain lesions in a multidisciplinary setting.

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SpringerNeurosurgery

**H.-J. Reulen (ed.)
in collaboration with J. Brennum, Fl. Gjerris, J. Haase, W. Kanpolat, D. Lang. K. W. Lindsay, J. Lobo Antunes, D. W. Long, G. Neil Dwyer, G. Schackert, J. Steers, H. J. Steiger, J. C. Tonn, T. Trojanowski, P. A. Winkler**

Training in Neurosurgery in the Countries of the EU

A Guide to Organize a Training Programme

2004. VIII, 125 pages. 4 figures.
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ISBN 3-211-21322-8
Acta Neurochirurgica, Supplement 90

Agreed standards and guidelines are the heart and soul of improving the differing training systems and to harmonize neurosurgical training in the European countries. Such standards and guidelines have been laid down in the European Training Charter of the European Union of Medical Specialists and recently novellated.

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