Advances in the neurorehabilitation of severe disorder of consciousness

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Abstract

Introduction. The paper describes the evolution of knowledge concerning severe brain injury which determines the Vegetative State/Unresponsive Wakefulness Syndrome.

Background. The term Vegetative State was proposed by Jennet and Plum in 1972. Later on, the Intensive Care Units progresses increased the survival of these patients and, contemporarily, decreased their characteristic conditions of cachexia and severe dystonia. In 1994, the disease was conceived as a disconnection syndrome of the hemispheres from the brainstem, mainly due to a temporary or permanent deficit of the functions of the white matter. From 2005 on, the psychophysiological parameters relative to an emotional consciousness, albeit submerged, were described. Since then, it has been recognized that the brain of these patients was not only to be considered living but also working.

Conclusion. The latest studies that have greatly improved the knowledge of the physiopathology of this particular state of consciousness. These new insights have led to the formation of a European Union Task Force, which has proposed in 2009 to change the name from a Vegetative State to Unresponsive Wakefulness Syndrome, outlining the character of syndrome and not that of state, as forms of even late recovery in consciousness levels have been observed and described.

INTRODUCTION

In 1899 Rosenblath [1] described the first case of chronic coma who survived the trauma for eight months with artificial feeding through a nasogastric tube. Depiction of the patient lying passive, akinetic, with eyes open and unresponsive, was described for the first time in 1940 by Kretchmer [2] under the name of “apallic syndrome”. This describes very clearly a precise clinical concept. It is interesting to note that the status of the complex clinical syndrome was already recognized. In 1940, the definition of apallic syndrome expressed the decommissioning of the cerebral hemispheres as the pallium, that is, the cerebral cortex, is suppressed in its overall function. This decortication produces essentially a “mesencephalic being”.

The picture of post-traumatic brain damage that characterizes the apallic syndrome was defined in 1965 at the International Congress of Neurology in Vienna by Gerstenbrand [3]. The first work in Italian was published in the journal Sistema Nervoso by Dolce and Kaemmerer in 1966 [4].

This condition was also defined with different terms such as akinetic mutism [5], prolonged recklessness [6], hypertonic post-comatose stupor [7], parasomnia [8], the vigil coma [9].

All these definitions were included in the term “vegetative state” proposed by Jennett in Glasgow in 1972 [10], overcoming the proposals of the school of Bordeaux and of Loewenstein – Tel Aviv.

We can identify three periods in the history of the vegetative state (VS). The first period is that preceding the opening of intensive care units (in Italy around 1970). The second period ends with the progressive establishment of units able to hospitalize the patient early on: semi-intensive care units and units for severe brain injury. In Italy this began in 1994 with a first unit in Garbagnate set up by Prof. Soriani. Many years before in Verona, Prof. Bricolo opened a Coma Department.

Before being admitted to intensive care units, post-traumatic patients in a vegetative state were initially hospitalized in neurology or neurosurgery units, where many studies were produced. In this period particular importance was paid to neurological examination and subsequent anatomopathological confirmations. In particular, Gerstenbrand describes in detail the full clinical picture and its evolution through various “transition syndromes” that express the functional level reached during the reorganization process [11].

According to various authors, functional exploration by EEG and evoked potentials and the study of the organization of sleep allow evolution to be predicted and allow for a prognosis. The onset of paradoxical sleep was acknowledged as a favorable prognostic [12]. In particular, early works in the ’60s put much emphasis

Key words

- disorders of consciousness
- vegetative state
- unresponsive wakefulness syndrome
- heart rate variability
- central autonomic network

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on a number of neurological signs and reflexes of the brainstem. When intensive care units became operational, case studies increased and this approach was practically abandoned as all observations were relative to single cases’ prognosis only.

Mortality dropped drastically, nursing especially nutrition, improved. No more extreme cases of weight loss with the typical aspects of cachexia were observed. Some late complications signs such as that of Klippel, pursed mouth, the rabbit-snout phenomenon, as well as pictures of extreme pathological postures become rare. On the other hand, neurological studies and clinical instruments decrease in literature. In Italy the third phase began in the years 2000, ten or more years later than in France, Austria, England, or, especially, Israel. It is characterized by the opening of units dedicated to taking care of patients with severe disorders of consciousness.

Not only does survival improve but, above all, so does outcome. Studies that lead to a true advancement of knowledge of this severe brain damage that represents a possible evolution of coma – which is never chronic, lasting more than 3-4 weeks, and ending with eye opening and progressive organization of sleep as registered with EEG – begin. A milestone in the evolution of knowledge concerning the vegetative state is constituted by the publication in 1994 in the New England Journal of the results of the task force that the American president of the United States had commissioned to several scientific societies [13]. This initiative was taken following the great impact on American public opinion that some cases such as those of Paul Prophy, Karen Ann Quinlan, and Nancy Cruson regarding the question of active suspension of respiration, improved. No more extreme cases of weight loss with the typical aspects of cachexia were observed.

A key aspect of this document, which still constitutes a reference point, is the finding that patients in a vegetative state are not able to relate to the outside world from which they remain isolated even if the vital functions can be autonomous.

Persistent vegetative state is recognized in that it lasts for at least a month and is permanent. Just two years later in 2006 the London Conference puts forward an important correction by strongly recommending not to use the terms persistent and permanent as this last term would have implied an ultimate conviction.

Rare cases of recovery of consciousness activities, even partial, and even after a year were already being described. One started to speak about “minimal responders” and in 2002 Giacino [14] describes in detail a particular condition in which minimal responses are indicative of a state of initial recovery of consciousness. This condition was defined as minimally conscious state (MCS).

From the years 2000 on the scientific community in Italy expresses a great interest for this type of severe disorders of consciousness. Units dedicated to taking care of patients in VS or SMC are opened all over the country. They are differently named such as Semi-intensive care unit of the Neurorehabilitation or Unit for severe brain injury. The number of beds is today sufficient even if precise and uniform guidelines that establish a common minimum standard are lacking.

In addition to three Consensus Conferences organized by SIMFER (Italian Society of Physical Medicine and Rehabilitation) the Ministry of Health has set up four ministerial committees on the VS and MCS: they are the Veronesi, Sirchia, Di Virgilio and Roccella Commissions. Lastly, the document of the State-Regions Conference of 2012 with specific provisions has been drawn up.

Finally, the Ministry of Health has established in 2012 a working group for the care of people in a vegetative or minimally conscious state with the task of verifying whether the regions have enacted and proceeded to organize the contents of the Conference of State-Regions document.

FROM CLINICAL EXPERIENCE TO RESEARCH

Dolce and staff publish in 2012 the results of the recovery in a semi-intensive care unit of a series of 722 cases [15]. A real turning point in the reflection concerning the vegetative state takes place in 2002 when Dolce and Sazbon speak of the “inner world” of the patient, for the first time. This against all literature that had been limited to dealing with the patient’s relationships with the outside world [16].

This first hypothesis bred an activity of scientific research with the use of different experimental approaches [17].

A first work in literature that speaks of submerged emotional activity describing the “mom effect” was published in 2005 by Dolce [18]. In 2006 Owen’s famous study was published in Nature. It highlights the islands of active cerebral cortex using fMRI [19, 20]. Subsequently, collaboration of top research centers in Cambridge and Liège developed many more case-studies.

In the last decade, after the Aspen Group [14] publication one has witnessed an exponential growth of literature both as regards nosology and as regards the use of new technologies (PET, fMRI, neurophysiopathology) apt to support vegetative state clinical diagnosis [21].

Besides investigations with instruments, there have been several studies aimed at improving the clinical diagnosis using validated scales. The high percentage of misdiagnosis [22-24] is mainly caused by problems of method valuation. It has been shown that standardized neurobehavioral assessment using the CRS-R is a more sensitive means for differential diagnosis in patients with disorders of consciousness when compared to diagnoses determined by clinical consensus [25].

It is also necessary that such assessments be done at different time moments as it has been shown that a fluctuation of the activity of consciousness in the course of the day occurs [26].
NEUROPHYSIOPATHOLOGICAL HYPOTHESIS OF CONSCIOUSNESS

Notwithstanding new knowledge and production in recent years of an abundant literature on the vegetative state and MCS which register an improvement not only of survival but also of outcome – especially in patients with traumatic acquired injury – the therapeutic approach has always been characterized by a marked empiricism lacking any scientific evidence. Not only have none of the methods been validated but they have not even been compared with others, and the actual effectiveness of each maneuver has not been ascertained.

The vast empirical experience has, however, led to the recognition of the validity of certain rules. The method of sensory bombardment has been abandoned. On the other hand it is recognized that before each stimulus it is necessary to obtain the “relaxation” of the patient in order to obtain a first consistent response. It has been tried to obtain it with hydrotherapy in hot water at 30 °C while playing special relaxing music. It is really strange, to say the least, that therapy aimed at obtaining the recovery of such an important function as the activity of conscience has remained entrusted to a purely empirical approach without a scientifically valid background.

Thus, in 2003 the need was felt to build a RAN (research in advanced neurorehabilitation) research laboratory to study the physiopathology of the VS, in order to use knowledge derived from it to proceed on a scientific basis for the development of a targeted therapy.

It was first of all necessary to have a theory of consciousness in order to satisfy demands deriving from a scientific approach to the experimental study of a still uncertain subject. From a strictly neurological point of view, consciousness is understood as “the functional state of the brain that allows all of the other functions”.

In accordance with the theory of coherence, this condition occurs only when four specific conditions are met simultaneously and with a certain degree of interaction [27]:

• presence of specific sensory inputs;
• presence of non-specific, diffuse input from ascending reticulothalamic activating systems diffusely projecting to the cortex;
• cortical activity with neuronal discharge in the medium-frequency range;
• activation of the primitive ipsilateral and contralateral motor systems, which stabilize spatial relationships and orient the system toward the source, thereby allowing for perception.

THE NEUROPHYSIOPATHOLOGY OF THE LABORATORY OF CONSCIOUSNESS

It started from an occurrence derived from observations by family members, especially mothers, which we thought impossible. They reported with doggedness to have observed behavioural responses in their children, responses which we rather ascribed to emotional component.

We have paid little or no relevance to these continuous and urgent observations of family members for decades. One day in 2003 during professor Sazbon’s internship at our institution, a mother came to refer that her child had definitely recognized her. We went to verify what reported, but, as usual, we were not able to objectify any appreciable sign.

A discussion of the episode, which occurs so often in family members of such patients, ensued.

We were agreed, on the basis of decades of experience and of our vast experience that patients in a vegetative state were not able to give any consistent response, as is universally known. But on this occasion we took note that, in the end, we were denying a behavior that had never been studied with a scientific experimental approach. The first spark of what led to a fruitful intense research spanning over 10 years had been lit.

In a first work we recorded in polygraphy the EEG, the EMG, heart rate variability, and the psychogalvanic reflex. Family members of patients in a vegetative state who claimed to have observed behavioral responses of their loved one were instructed to speak in a certain way to the patient for 10 minutes during polygraphy clearly naming some people and describing situations that were known to be particularly dear to the patient. After two minutes of rest the same speech was repeated by another person instructed ad hoc but not known by the patient. The experiment was repeated four times.

Significant changes were recorded in 13 patients, in particular psychogalvanic reflex and HRV (heart rate variability), but these were not always repeatable. The effect named “mom-effect” was interpreted as being the recording of the physical correlates of an emotion [18], and therefore attributable to an activity of the submerged emotional brain.

The unclear interpretation of the psychogalvanic response led to a redefinition of the experimental set. Sixteen healthy subjects with no experience in listening to classical music were required to listen many times, not in sequence, to extracts of 5 minutes’ duration (corresponding to about 300 heart beats) of four songs (Quintet, Op. No. 11. 5, by L. Boccherini; Minuet; Pathetic Symphony by P.I. Tchaikovskv; St. John’s Night on the Bald Mountain, by MP Mussorgsky; Morning by E. Grieg; Peer Gynt, Op. 23) inviting them to express their mood after listening of each piece of music. Emotions expressed were differentiated as positive and negative, ranging from anger to happiness, from anguish to serenity. The results of HRV analysis were associated with the emotions described showing a correlation between emotions and HRV. The same procedure was repeated with subjects with good (LCF > 8) cranial trauma outcome and observing a correlation between emotional responses, tracks listened and HRV data [29].

The same experimental set was later repeated in nine patients in vegetative state and correlation between the proposed songs and HRV results comparable to those recorded in healthy subjects observed, especially in the passages referred to Boccherini and Mussorgsky [30].

The model extracted from listening to music was applied to the data obtained with the “mom effect”. Values for the analysis of HRV were taken to be equivalent to a positive emotional attitude in the presence of family member and of a negative emotional attitude in the presence of the control subject.

These results allowed to conclude that the patients in...
the perception of pain in VS and MCS patients was described. The International Association of Pain defines the pain as “an unpleasant sensory and emotional experience. The program designed to verify the effectiveness of an intensive sensory stimulation program. The topic is one of the research lines developed and carried out in collaboration with the Coma Science Group, Cyclotron Research Center University of Liège and the Fudan University in Shanghai.

The multicentric study (RAN – S. Anna Institute of Crotone; Coma Science Group of Cyclotron Research Center, University of Liège; International Vegetative State and Consciousness Science Institute, Hangzhou Normal University, Hangzhou, China) regarded VS/UWS and MCS patients in acute and chronic phases. The program provides standardized methods and timing of application and involved the stimulation of the patient through the five sensory channels. In the patients undergoing to the stimulation program, the improvement in the level of consciousness could be showed by the behavioral scales assessments and the neuroimaging correlates (the related paper is under review in Annals of Neurology).

PAIN
As a collaboration with the Coma Science Group, Cyclotron Research Center of the University of Liège, a second research line on the assessment and the study of the perception of pain in VS and MCS patients was defined. It is very difficult to assess the nociception in severe brain damaged patients with disorder of consciousness. The International Association of Pain defines the pain “... an unpleasant sensory and emotional experi-
ence associated with actual or potential tissue damage, or described in terms of such damage. Patients with altered state of consciousness (VS and MCS) are not able to report such experience through verbal or non-verbal reports. Based on this, we referred to the concept of nociception, and not to that of pain, defined as “An actually or potentially tissue-damaging event transduced and encoded by nociceptors” [41].

In several studies was showed that in MCS patients, unlike the VS patients, there may be a pattern of brain activation that is comparable to that of the control group, in response to the nociceptive stimulation [42, 43].

There are several standardized scales for the detection of behavioural signs of the perception of nociceptive stimuli in non-communicative patients, such as infants or elderly with dementia, but none is specifically applicable to VS or MSC patients. The nociception coma scale (NCS), is a sensitive suitable tool for the evaluation of the perception of nociceptive stimulation in severe brain damaged patients and/or with disorders of consciousness.

The validation study of the NCS showed a high degree of concurrent validity, with other four validated scales (NIPS, FLACC, PAINAD, CNPI), a high degree of internal validity and sensitivity [44].

Starting from the concepts already demonstrated, the objective of further study of S. Anna Institute, in collaboration with the Coma Science Group, is to demonstrate the high diagnostic sensitivity of NCS [45].

The Sensory Regulation Laboratory of the RAN, currently leads among others a study aimed to investigate the possibility of learning the nociceptive stimulus in VS/UWS patients, according to the theoretical criteria of operant conditioning.

AMBIENT INTELLIGENCE

Ambient intelligence (AmI) allows real-time automatic recording of biological/medical information and environmental data. It is extensively applicable in the patients’ monitoring and in medicine and neuroscience research requiring large biomedical datasets, e.g. in the study of spontaneous or condition-dependent variability or chronobiology [46]. In this respect, it is equivalent to a traditional laboratory for data collection and processing, with minimal dedicated equipment, staff and costs; it benefits from the integration of artificial intelligence technology with traditional/innovative sensors to monitor clinical or functional parameters [47].

A prototype AmI platform (MIMERICA*) has been implemented and is operated in a semi-intensive unit for the vegetative and minimally conscious states to investigate the spontaneous or environment-related fluctuations of physiological parameters in these conditions.

The facility MIMERICA* has been engineered and a prototype is operated for monitoring and acquisition of data with relevance in neuroscience and medical research in a dedicated semi-intensive care unit for the severely brain injured, in coma, or in the vegetative or minimally conscious states [48, 49]. It combines sensors for the ambient (temperature and humidity, CO₂, light/dark cycles, noise) and for each subject’s relevant parameters (body temperature, heart rate and systolic/diastolic blood pressure, breathing, pO₂, pCO₂, spontaneous movements, voice, eye movements and eye blinking). Spontaneous or stimulus-/event-related brain signals and the heart rate variability can be recorded as well.

The subjects’ data are acquired by sensors at predetermined short time intervals and pre-analyzed in biometric nodes. Raw or pre-treated data are sent through wireless connections to a gateway also acquiring environmental measurements for storage and further processing. Information from the subjects and environment is transferred to the AmI Core System and central database by safe intranet or internet connections and stored for further analyses.

CONCLUSIONS AND FUTURE DEVELOPMENTS

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From a pathophysiological point of view, SV/UWS is characterized by a syndrome of disconnection between the brain and the brain stem caused by two different mechanisms: the traumatic tear of the output dendrites of the neuron in the area of the collar which constitutes the condition described by Adams and Giannarelli as diffuse axonal injury that produces an irreversible anatomical damage.

The same effect can however be caused by damage of the white matter due to the effects of cerebral edema and intracranial pressure at the time of the acute event, but also by a late illness of white matter of substantially dysmetabolic nature.

It is not so much the neural damage which supports the clinical syndrome of disconnection but rather the damage of the white matter which prevents connection between the various structures. In this case, future possibilities of recovery today unthinkable lie ahead. The mechanisms that determine the non-reconstruction of neurites at central level, as is the case for the peripheral nervous system, have been known for over 10 years.

The cause of this process has already been identified in a betalipoprotein that inhibits the growth factor [50-53].

It is therefore likely that ongoing studies may lead to a truly innovative and far-reaching therapeutic success. In addition to anatomical reconstruction, which is the most desirable premise for each form of therapy, other potential interventions designed to dramatically improve the functional recovery of such serious conditions affecting patients in VS can be foreseen.

Improvement in emergency medicine and the advancement of the therapeutic approach to neuroprotection in the acute phase on the one hand, but also new methods of rehabilitation of consciousness with sensory regulation and the application of ambient intelligence are all other perspectives that allow one to shed a new light on the future evolution of this devastating disease, not only for the patient but for all family members and the subsequent fallout aspects of social damage.

Finally, we would like to emphasize how important changing the name of the first brain damage from vegetative state to unresponsive wakefulness syndrome [54] has been from the methodological point of view in order to assist evolution
of scientific thought: A permanent state does not provide for the possibility of evolution, as against a syndrome which can evolve positively also in a substantial manner. It has been this passionate involvement that led us to convene a European Task Force at the Ministry of Health in Rome, who comforted us in sharing and promoting a necessary and indispensable new way of thinking to start real progress.

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**Conflict of interest statement**

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Submitted on invitation. Accepted on 27 June 2014.

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