Percorsi clinici in Neuroscienze

A cura di: E.C. Agostoni, A. Salmaggi, D. Consoli, B. Zanotti

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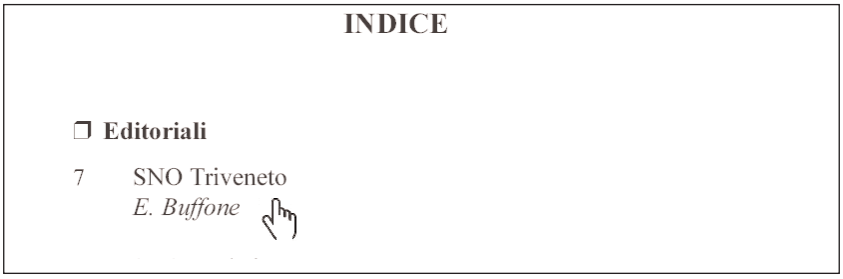

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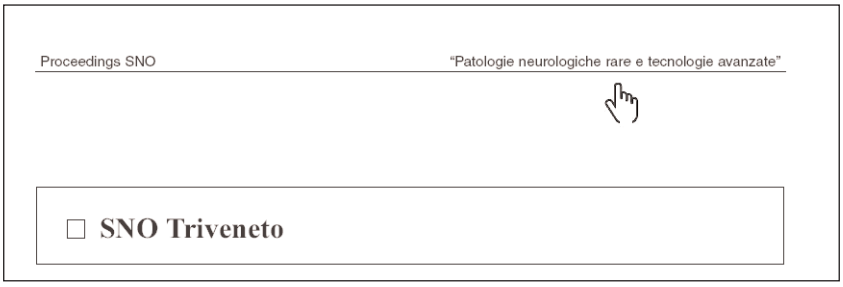

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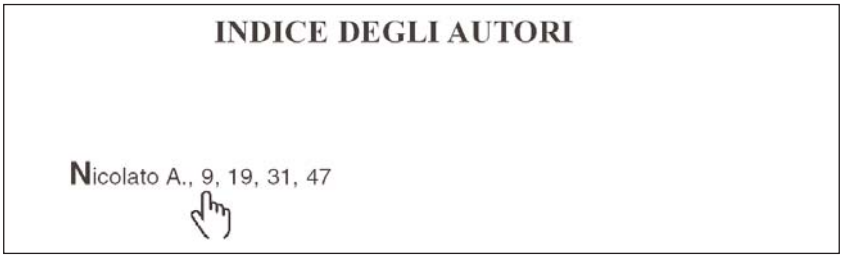

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PERCORSI CLINICI IN NEUROSCIENZE

A cura di:
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Presentazione

Lo scenario delle Neuroscienze è sempre più ricco di innovazioni scientifiche, cliniche e tecnologiche. Sempre più valore rivestono i casi clinici che hanno percorsi complessi nei Dipartimenti di Neuroscienze, nell'ambito di un singolo ospedale o che necessitano di una gestione integrata tra più ospedali. Spesso le linee guida non coprono esaustivamente lo scibile delle conoscenze necessarie per la gestione di casi clinici complessi. La sussidiarietà delle competenze professionali neurologiche, neurochirurgiche, neurointensivistiche, neuroradiologiche e neuroriabilitative è integrata con le competenze degli infermieri, dei tecnici della riabilitazione e della diagnostica strumentale neurofisiologica.
I "Clinical Round" SIN e SNO 2019 si propongono con un formato innovativo che risponde alle nuove esigenze di una gestione sempre più complessa dei casi clinici.
La prima parte della giornata è infatti articolata con la presentazione multidisciplinare dei casi clinici a cura di diverse figure professionali operative nell'ambito delle Neuroscienze.
Nella seconda parte della giornata vi è lo spazio per la presentazione libera di casi clinici nell'ambito delle Neuroscienze.

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Case report CASI CLINICI MULTIDISCIPLINARI

□ Myasthenia and thymoma: integrated management and team strategy

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□ INTRODUCTION

Myasthenia Gravis (MG) is an antibody- mediated chronic disorder that affects neuromuscolar junction altering neuromuscolar transmission and leads to skeletal muscle weakness and fatigability. Usually MG in divided into subgroups regarding clinical features and serum antibodies with implications for diagnosis, treatment and prognosis. Most of the patients have antibodies against the nicotinic AcetylCholine Receptor (AChR), less frequently MUscle-Specific Kinase (MUSK) or LRP4 (low density Lipoprotein Receptor related Protein 4).
The thymus is checkpoint organ for autoimmunity in AChR myasthenia. The relationship between MG and thymoma in well documented, approximately 15% of patient with MG are found to have thymoma, and 20-25% of patient with thymoma have MG.
Thymoma associated with MG in identified as a tumor originating from thymic epithelial cells (World Health Organization: WHO type B). WHO histological classification B2-B3 and Osserman stage IIA-IV are independent predictors for post-operative myasthenic crisis in patients undergoing total thymectomy.
MG associated with thymoma in equally common in men and women and occurs at any age with a peak onset around 50 years. Juvanile Myasthenia Gravis (JMG) is defined presenting before the age of 18 years. Very frequently JMG presents with the involvement of the oculomotor muscles, with or without generalized involvement.
Treatment of MG consists in acetylcholinesterase inhibitors such as pyridostigmine, main agent used whether in children or adults. Even the appropriate usage and dosing of pyridostigmine symptoms and signs of MG may continue. If necessary pyridostigmine may be combined with immunosuppressive agents, most commonly prednisone. Prednisone is easily administered in children and adults, but long-term use can be harmful due systemic side effects. Azathioprine can be considered for immunosuppressive use in MG.
Immune Globulin IntraVenous (IGIV) con be administered for MG in an effort to reduce the circulating autoantibodies; Plasma EXchange (PEX) can also be used to filter antibodies and cytokines from serum. A comparison between IGIV and PEX showed no significant difference between the two treatments.

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There is some evidence that pre-thymecthomy PEX improves short-term post-operative outcomes of myasthenia gravis (need for mechanical ventilation and Intensive Care Unit stay). This effect is due to the huge amount of antibodies removed from the intravascular site during PEX.
Thymectomy in indicated for patients with seropositive AChR myasthenia and has been found to be associated with improve remission rates.

□ CASE REPORT

We report herein the case of an 18-year-old Caucasian woman entered into our hospital for appearance of dysphonia for several months during speech and worsening dysphagia. She soon developed weakness of neck and proximal muscle. Neurological symptoms were treated with pyridostigmine at maximal dose with partial control. We administered a cycle of IGIV 2 g/kg in five days without improve of symptoms.
She had an extensive workout with spine and brain MRI, autoimmune studies which were normal. Detection of AchR serum antibodies was elevated at 43.2 pmoli/ml. Repetitive nerve stimulation study reveals 50 percent of decrement in amplitude of muscle action potential in several nerves after facilitation (ulnar, median, facial ad accessory nerve).
A chest CT showed the presence of solid tissue in antero-superior mediastinum, immediately caudally to epiarotic vessels, and also extends to the middle mediastinum, with greater prevalence on the left. No dissociability of the lesion from the anterior chest wall, from the adjacent lung parenchyma and from the pericardium.
The chest lesion was biopsy and histological exams showed neoplastics epithelial cells (CKAE1/AE3+, CK19+, p63+/-) mixed with T lymphocytes (CD3+, CD5+, TdT+) and rare B lymphocytes (WHO classification thymoma B2).
Her condition deteriorated with increasing weakness, difficulty in chewing, walking and standing, and with appearance of dyspnoea.
She was diagnosed with locally advanced B2 thymoma and myasthenia gravis. According to clinical stage cT3N0M0 (Masaoka stage IV a) the patient received neoadjuvant chemotherapy with Cyclophosphamide, Adriamycin and Platinum (CAP) combination chemotherapy. During first cycle, drug infusion was complicated by a myasthenic crisis that required tracheal intubation. Chemotherapy administration was resumed on mechanical ventilation and completed without further acute adverse events. Febrile neutropenia occurred afterwards and was treated according to guidelines.
we suspected a sudden and weighty increase in antibodies title due to thymic cell necrosis after chemotherapy. Thus, we decided to perform urgent PEX, at day 11 after the first cycle of CAP and to schedule successive every-two-other day PEX, set for 1 plasma volume to be replaced with 5% albumin. We treated the patient with the same schedule also before and after the 2nd cycle of PAC and performed a total of 9 PEX, the last of them 5 days before surgery. The patient safely undergone thymectomy, after which PEX were no longer necessary.
A second cycle of chemotherapy was administered without major complications. CT-scan showed Response Evaluation Criteria In Solid Tumors (RECIST 1.1) Partial Response (PR). Hence, the patient underwent extended thymectomy, left upper lobectomy and subtotal pericardiectomy with radical tumor resection (R0). The patient was then treated with adjuvant radiotherapy on mediastinum and is currently in remission (No Evidence of Disease: NED). Neurological symptoms are under control with therapy. Follow-up is ongoing.

□ DISCUSSION

Several retrospective studies have been conducted to identify variable that influence the natural story of myasthenia associated with thymoma.
Studies demonstrated that early onset age before 45 as well as invasive thymoma were significantly associate with poor prognosis and persistence of symptoms.
Only complete resection of thymoma was significantly correlated with a better prognosis.
The incidence of young patients with MG and invasive thymoma is extremely sporadic and is necessary multi-disciplinary approach in managing of disease.
We were successful thanks to an early diagnosis and an immediate treatment of the patient. Plasmapheresis concomitant with chemotherapy has reduced the number of myasthenic crisis. Neoadjuvant chemotherapy reduced the tumor mass making a complete resection of the thymoma possible.
Collaboration between neurologist, oncologist and ematologist provide a favorable outcome of our patient.

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Case report CASI CLINICI MULTIDISCIPLINARI

A cerebellopontine angle tumor in a patient over 80 years old

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SUMMARY: *INTRODUCTION. The treatment of cerebellopontine angle tumors in aged patients must be balanced against age-related contraindications and issues related to the quality of life. We report a case of uneventful resection of a large cystic vestibular schwannoma in a patient over 80 years old.*
CASE REPORT. A female patient 83 years old was admitted to the hospital for imbalance, hearing loss and frequent falls in the previous months. The functions of the other cranial nerves were normal. Magnetic Resonance Imaging revealed a Koos 4 vestibular schwannoma in the left cerebellopontine angle (Koos et al., 1993). The tumor showed a lateral solid and a medial cystic component, compressing and displacing the brainstem. The patient was operated by a suboccipital retrosigmoid approach, with intraoperative neurophysiological recordings. The facial nerve was identified by Electromyography and its fibers appeared to be diffusely adherent to the capsule of the cyst. The resection was limited to the solid component and the cyst was just decompressed. Facial nerve function was preserved. The patient achieved a good outcome.
DISCUSSION. We report a case of a large cystic vestibular schwannoma in a patient over 80 years old, who presented with total hearing loss and clinical signs due to severe brainstem compression. Surgical treatment was assisted by extensive intraoperative Electromyography, that helped to preserve the facial nerve. The patient achieved a good recovery.

KEY WORDS: *Cerebellopontine angle, Facial nerve, Intraoperative neurophysiological monitoring, Neurosurgery, Vestibular Schwannoma.*

INTRODUCTION

Vestibular Schwannomas are the most frequent tumors in the CerebelloPontine Angle (CPA), being benign tumors and allowing for 70-90% of tumors in this region[3]. The surgical treatment of CPA tumors in elderly patients must be balanced against age-related concerns and the risks of postoperative complications, negatively affecting their residual functional capacity. The rate of postoperative complications of vestibular Schwannoma surgery strongly relates to the size of the lesion and to its adherence to the surrounding neurovascular structures. The facial nerve is exposed to the risk of surgical injury, due to its anatomical relation with the tumor.

We report a case of a large cystic vestibular schwannoma in a patient over 80 years old, harboring a Koos 4[2] lesion in her left CPA. A subtotal resection had been planned, due to the patient's age. The neurosurgeon extensively applied intraoperative Electromyo-

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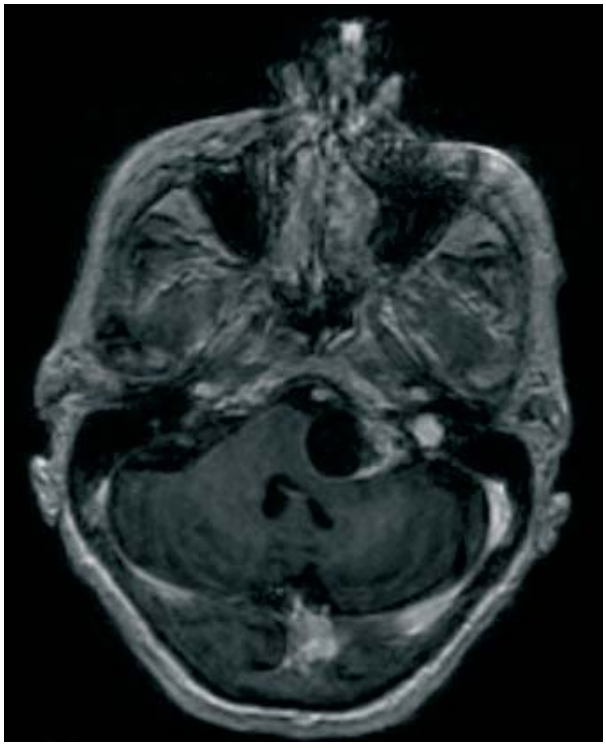

Figure 1. MRI showing an extra-axial lesion in the left cerebellopontine angle, with a mass effect on the brainstem and the fourth ventricle. A solid enhancing portion extended in the internal acoustic meatus and a medial cystic portion (2.5 cm diameter) compressed and displaced the brainstem.

graphy to map the cranial nerves in the surgical site, and he found that fibers of the facial nerve were adherent all over the medial part of the tumor. The surgical strategy was then modified, leading to brainstem decompression and preservation of the facial nerve.

□ CASE REPORT

A female patient 83 years old was admitted to the hospital for imbalance, hearing loss and frequent falls in the previous months. Her mental status was normal for her age and she was in good general medical status. Hearing loss was bilateral, but worse on the left side. No deficits of other cranial nerves were observed. Dysmetria, poor balance, ataxic gait and mild hyperreflexia on the left side were present.
MR imaging showed an extra-axial lesion in the left cerebellopontine angle, with a mass effect on the brainstem and the fourth ventricle. A solid enhancing portion extended in the internal acoustic meatus and a medial cystic portion (2.5 cm diameter) compressed and displaced the brainstem (*Figure 1*).
The patient was operated by a suboccipital retrosigmoid approach, with intraoperative neurophysiological monitoring. Somatosensory and motor evoked potentials were recorded. Free running and triggered Electromyography from the facial muscles, masseter, trapezius and genioglossus muscles were available. The neurosurgeon tracked the motor nerve fibers in the operating field by a surgical aspirator or a dedicated probe, both delivering constant current electrical stimulation[1,4]. When the neurosurgeon stimulated the medial cystic component of the tumor, widespread electromyographic responses in the facial muscles were triggered from the whole surface of the capsule. Then, a site where less facial muscle responses were evoked was chosen to enter the cyst. A small puncture allowed the cyst to collapse and the resection was limited to the solid portion of the lesion. Postoperative CT scan showed the collapsed cyst. The facial nerve function was maintained, and the patient achieved a good postoperative recovery.

□ DISCUSSION

We report a case of a large cystic vestibular Schwannoma in a patient over 80 years old, who presented with total hearing loss and imbalance, in whom the earliest clinical signs of a vestibular Schwannoma were possibly dismissed as age-related troubles, delaying the treatment until the lesion achieved a large size (about 4 cm) and the patient suffered from severe brainstem compression. The tumor had a solid portion, that extended in the internal acoustic meatus and a medial cyst that compressed and displaced the brainstem. Motor fibers of the facial nerve appeared to be diffuse on the whole surface of the capsule, as shown by intraoperative Electromyography. A subtotal resection had been planned, due to patient's age, but the final decision favored a decompression of the cyst, by entering its wall in a site negative to stimulated EMG. Facial nerve function was preserved. Postoperative CT scan showed the collapsed cyst. The patient achieved a good outcome and a good recovery of balance.

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Case report CASI CLINICI MULTIDISCIPLINARI

□ Neurological complication of immune checkpoint inhibitors: pembrolizumab-related encephalopathy

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SUMMARY: *The recent use of immune checkpoint inhibitors for cancer therapy brought out different side.effects, including neurologic ones. It is essential to recognize and to treat the neurologic immune-related adverse events as soon as possible, to increase the odds of a complete recovery. We describe a patient with immune-encephalitis pembrolizumab-related: the multidisciplinary approach allowed the prompt recognition and timely therapy with rapid improvement and full recovery. A protocol for multidisciplinar diagnosis and management will be helpful.*

KEY WORDS: *Immune checkpoint inhibitors, Immune encephalitis, Neurological adverse events, Pembrolizumab.*

□ INTRODUCTION

Immune checkpoints are molecules involved in the maintenance of immunologic homeostasis and they are crucial to prevent the development of autommunity diseases and maintain self-tolerance.
CytoToxic Lymphocyte-Associated protein 4 (CTLA-4) and Programmed cell Death 1 (PD-1) are two of these molecules that inhibit an immune response and they are recently used in clinical management of different oncologic diseases, including Hodgkin lymphoma (HL).
Inhibition of CTLA-4 and PD-1 may increase a baseline T cell-specific immune response against the tumor, leading to imbalances in immunologic tolerance and resulting in excessive immune response.
Every organ or tissue in the body can be the targeted by deriving inflammatory or adverse events.

□ CASE REPORT

We describe the case of a young man, 24 years old, suffering from a Hodgkin lymphoma. He underwent chemotherapy (from December 2017 to April 2018), biological therapy with pembrolizumab (an antiPD-1 molecule) in August 2018 and bone marrow transplantation in January 2019.
In June 2019 he complained confusion, language difficulties and right haemiparesis, with insidious onset in the previous weeks. Focal seizures in the acute phase occurred.
Brain MR imaging showed remarkable signs of white matter alterations, cerebro-spinal fluids showed normal white count cell[(1)] and total protein at 154.9 mg/dL, while ElectroEncephaloGraphy (EEG) showed delta slow wave in the left hemisphere.

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These findings and discussion of the case with both neurologists and onco-hematologists lead to interpret clinical manifestation as immune pembrolizumab-related encephalopathy. An extensive panel of laboratory and imaging tests was performed (including paraneoplastic antibodies research), and other causes of encephalitis were excluded.
High-dose steroid and following oral steroid therapy was performed, with rapid and progressive clinical improvement, with only slight tremor in the hands after 3 weeks. Control EEG after 40 days was normal. Brain MR improved and 6 weeks later no alterations were found. Oral steroids were slowly tapered. Follow-up at 5 months shows a complete recovery.

□ DISCUSSION

Adverse events are observed in 5-10% of patients treated with PD-1 inhibitors and immune adverse events can occur late after initiation of therapy or even after treatment discontinuation.
The most frequent neurological complications (1-12%) related to the biological therapy with immune checkpoint inhibitors are both peripheral and central nervous system diseases. Enteric neuropathy and myasthenia were also described.
Median time from Immune Checkpoint Inhibitors (ICI) initiation to encephalitis onset is longer in patient receiving pembrolizumab than in patients receiving different molecules.
In the described patient, immunosuppression with ciclosporine after transplantation could have an additional role to explain the long window between the treatment discontinuation and the neurological manifestation.
Clinical symptoms of encephalitis induced by immune checkpoint inhibitors do not differ from those due to other causes. So an extensive panel of laboratory and imaging tests is needed to exclude other causes of encephalitis. Early recognition and treatment of neurological adverse events related to therapy with immune checkpoint inhibitors is essential to increase a complete recovery. In our patient, the multidisciplinary approach allowed the prompt recognition and timely therapy with rapid improvement and complete recovery. We are preparing a protocol with multidisciplinary approach and management of patients using biologic therapy.

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Case report CASI CLINICI LIBERI

□ Mesial frontal epilepsy manifesting with speech arrest: a case report

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SUMMARY: *INTRODUCTION. Electroclinical manifestations of frontal lobe epilepsy vary significantly depending on precise localization of seizure origin. Supplementary sensory-motor area and pre-supplementary sensory-motor area are located on the medial face of frontal cortex. Activation of the latter has been demonstrated during tasks that require inhibiting responses or switching between tasks and in the selection of words to be produced. Focal cortical dysplasias are frequently pharmaco-resistant and they emerge as one of the most important pathological substrates of surgically remediable epilepsies.*
CASE REPORT. We report a case of a 40 years old female who presented to our attention because of a pharmaco-resistant epilepsy since the age of 8. Seizures were described as characterized by paresthesia of the head and mainly of the left limbs and speech arrest with language production disturbance. Comprehension was unimpaired during the seizure. A video-EEG recording suggested a left fronto-central onset of the seizures. Brain MR imaging scan was concordant with such finding, showing a T2 hyperintensity in the left pre-supplementary sensory-motor area. On the basis of the anatomo-electro-clinical correlations, a lesionectomy was performed and histology demonstrated an International League Against Epilepsy type IIB focal cortical dysplasia. The patient, at a 4 years follow-up after the surgery, is seizure-free.
DISCUSSION. When seizure semiology is concordant with EEG findings, a structural cause of epilepsy should be suspected and performance of brain MR imaging scan is warranted. It must be kept in mind that pharmaco-resistant epilepsies due to focal cortical dysplasia type IIB are associated with excellent post-surgical outcome.

KEY WORDS: *Epilepsy, Pre-supplementary sensory-motor area, Speech arrest, Supplementary sensory-motor area.*

□ INTRODUCTION

Given the broadness of the frontal lobe, which represents 35-40% of total brain volume, its complex connectivity with multidirectional intra- and extralobar cortico-cortical efferent pathways and the large portion of ventromedial cortex far from EEG scalp electrodes[3,8], in the frontal lobe the electro-clinical localization of seizure onset can be challenging. Pre-Supplementary Sensory-Motor Area (pre-SSMA) is located on the medial face of the frontal lobe, as anterior part of the Supplementary Sensory-Motor Area (SSMA) localized in front of the leg representation in the motor strip. Pre-SSMA and SMA play an important role in motor control, processing somato-sensory informations and speech motor performance, espe-

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cially in the dominant hemisphere[1,5,6]. Focal Cortical Dysplasias (FCD) are recognized as being among the commonest causes of pharmaco-resistant epilepsies and when they are type II, the resection of the lesion yields a favorable long-term outcome[2,7].
Ictal language disturbance could be a pitfall localizing sign since it does not always indicate the involvement of the Broca's or Wernicke's areas.

CASE REPORT

A right-handed 40 years old female presented with drug-resistant epilepsy. Previous medical history was unremarkable, neurological clinical examination was normal and the patient was cognitively unimpaired. First seizure took place at the age of 8, with a bilateral tonic-clonic seizure at awakening. The patient was diagnosed with epilepsy and carbamazepine was started. She then had a seizure-free period of three years after which seizures recurred, only during sleep and described by awakening, choking and epigastric rising sensations sometimes followed by secondarily generalization. When the patient was 34, seizures began to occur also during wakefulness characterized by speech arrest without loss of contact and without understanding "impairment tingling" sensation of the head and of the left arm spreading to homolateral leg, rarely to contralateral limbs and post-ictal aphasia. We performed a Video-EEG monitoring during which several habitual seizures were recorded. Interictal EEG showed slow spikes and spikes and waves on F3-Fz, F3-C3, Fz-Cz with involvement also of the right side. Ictal EEG showed bursts of low/medium voltage fast activity mainly on F3-Fz, F3-C3, F7-F3 and Fz-Cz sometimes with contralateral spread, suggesting a left fronto-central onset. Brain MR imaging scan demonstrated a left T2-hyperintensity with transmantle sign in pre-SSMA. The patient underwent a left mesial frontal lesionectomy. After the surgery, she had a transient language disturbance characterized by increased speech latency, from which she progressively and completely recovered. Histology indicated a ILAE (International League Against Epilepsy) type IIB FCD. At a four-years follow-up visit the patient was seizure free (Engel Class I, ILAE)[4] and antiepileptic therapy was being gradually tapered.

DISCUSSION

Semiology of the seizures can be a diagnostic pitfall sometimes indicating many likely localizations, but it is determinant when analyzed on the whole of complete data.
Some areas are particularly difficult to be discovered as site of seizure onset.
When a FCD is recognized and anatomo-electro-clinical data are concordant, we suggest that epilepsy surgery could be an option to take into account given its remarkable favorable outcome in terms of seizures freedom.

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Case report CASI LIBERI

□ When DNA carries clinical case's solving

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SUMMARY: *INTRODUCTION. Trivial head trauma may be complicated by severe, sometimes even fatal, cerebral edema and coma occurring after a lucid interval ("delayed cerebral edema"). Mutations in the CACNA1A calcium channel subunit gene on chromosome 19 are associated with a wide spectrum of mutation-specific episodic and chronic neurological disorders, including familial hemiplegic migraine with or without coma. We investigated the role of the CACNA1A gene in one young man with delayed cerebral edema.*
CASE REPORT. A twenty years old man was admitted to emergency department a night after a head trauma reported during a party. Urgent CT scan revealed faded hemorrhagic signs and several bones fractures. The patient was alert and oriented, with a Glasgow Coma Scale of 15. He was then admitted to Neurosurgery ward and, after three days, together with a pyrexia of 40 °C, he neurologically worsened until a status of coma. He was transferred to Intensive Care Unit, intubated and ventilated. Since then his neurological conditions remained severe, while his neuroradiological findings dropped to cerebral edema and diffuse axonal damage. Only his familial history and genetic pattern could explain such a dramatic evolution.
DISCUSSION. Trauma-triggered "delayed cerebral edema" can be added to the wide spectrum of episodic and chronic progressive neurological disorders associated with CACNA1A mutations. Into the literature there are descriptions of S218L CACNA1A mutation, that renders subjects at risk for a cytotoxic edematous response to minor brain injury, mediated through dysfunction of neuronal voltage-dependent calcium channels. Screening for this mutation of the CACNA1A gene in our patient might be interesting. The novel S218L mutation and possibly other similar CACNA1A mutations are involved in a delayed disinhibited cytotoxic cerebral edematous response to minor head trauma after a lucid interval. This finding could offer new avenues for the understanding and treatment of this dramatic syndrome.

KEY WORDS: *Calcium channel, Cerebral edema, Mutations, Neurological disorders.*

□ INTRODUCTION

Trivial head trauma is sometimes complicated by severe, even fatal, cerebral edema and coma occurring after a lucid interval, a phenomenon referred to as delayed cerebral edema[14]. The syndrome has received particular attention in collision sports involving children and adolescents[18]. Apart from young age, no other risk factors are known[18]. Minor head trauma is also a recognized trigger of delayed migraine aura, also referred to as footballers migraine[17,21]. Particularly in children, these aura symptoms may be dramatic, including blindness, confusion, and impaired consciousness. Familial Hemiplegic Migraine (FHM)

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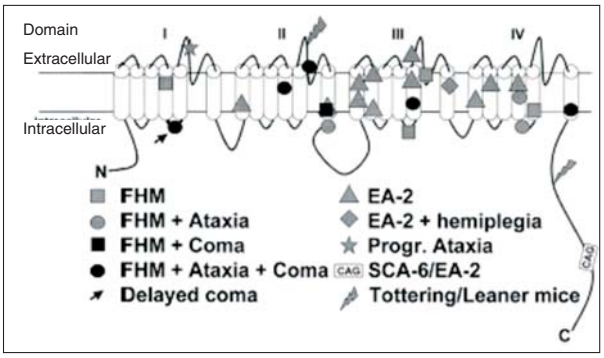

Figure 1. Localization of the novel S218L mutation in the α1A subunit of the P/Q-type calcium channel causing delayed cerebral edema and coma after a minor head trauma (*arrow*). The mutation is located in the small cytoplasmic between the fourth and fifth segments of the first domain of the protein. In addition, the localization of all other known CACNA1A mutations and the associated clinical phenotypes is depicted. FHM 5 familial hemiplegic migraine; EA-2 5 episodic ataxia type 2; Progr 5 progressive; SCA-6 5 spinocerebellar ataxia type 6 (*modified from Kors et al.* [14]).

is a rare autosomal dominant subtype of migraine with aura in which attacks are associated with hemiparesis[11]. Attacks of FHM can be triggered by minor head trauma, usually within 10 minutes[21], and may be associated with loss of consciousness, as in basilar migraine[9]. About half of the reported FHM families are linked to chromosome 19p13 and have missense mutations in the CACNA1A gene. This gene encodes the α1A subunit of a neuronal calcium channel that is primarily involved in mediating the release of neurotransmitters, including monoamines and glutamate[3,10,19]. Chromosome 19-linked FHM families report attacks that are triggered by head trauma or are associated with coma significantly more often than do non-chromosome 19-linked families[24]. Mutations in the CACNA1A gene are associated with a wide spectrum of neurological phenotypes, ranging from relatively mild episodic disorders, such as migraine[25], FHM[19], and episodic ataxia[19], to more severe permanent symptoms, such as progressive cerebellar ataxia and severe cerebellar atrophy[26,28].

CACNA1A is expressed at the neuromuscular junction and throughout the central nervous system, in particular in cerebellar Purkinje cells[22]. Functional studies of FHM1 mutations predict enhanced neuronal excitability and have shown increases in neuronal Ca^{2+} influx, neurotransmitter release and propensity to Cortical Spreading Depression (CSD)[6,27]. CSD is a brief (seconds) wave of intense neuronal and glial depolarisation that is slowly (2-5 mm/min) propagating over the cerebral cortex. A wave is associated with transient loss of membrane ionic gradients and by massive surges of extracellular potassium, neurotransmitters and intracellular calcium[22]. The depolarisation wave is followed by a potent relatively long lasting (> 20 min) neuronal suppression[7]. These electrophysiological and secondary molecular events are accompanied by transient neuronal swelling and loss of dendritic spines due to temporary tissue hypoxia[23], and cerebral oedema as a result of increased permeability of blood vessels through up-regulation of matrix metalloproteinases[8]. In humans, CSD is the likely underlying electrophysiological substrate of the migraine aura[15].

One particular type of CACNA1A mutation, the S218L mutation (*Figure 1*), was found in patients who suffered from particularly severe attacks of FHM which were triggered by trivial head trauma and were associated with often fatal excessive cerebral oedema[4,5,14].

Because of these clinical relationships and the remarkable diversity of neurological symptoms caused by CACNA1A mutations, we postulated a role for this gene in "delayed cerebral edema"[14].

We hypothesized that FHM1 gene mutations (e.g., the S218L mutation) may confer an increased risk of (symptoms of) Early Seizures and Cerebral Edema After Trivial Head Trauma (ESCEATHT), probably through increased susceptibility for CSD[22]. We discussed this in one patient with coma occurring after a lucid interval of a head trauma ("delayed cerebral edema") and in a subsequent review of the literature.

□ CASE REPORT

A twenty years old man was admitted to emergency department a night after an head trauma reported during a party with friends and with suspect assumption of alcohol, ketamine and MethyleneDioxy Metha-Amphetamine (MDMA). From his friends story he fell to the ground after a brawl. Urgent CT scan revealed thin striae of bilateral subarachnoid hemorrhage, a slight subdural hematoma, petechial hemorrhages and several bones fractures (*Figure 2*). Toxicological tests were positive for the presence of alcohol, tetrahydrocannabinol and paracetamol. Ketamine was not tested. The patient was alert and oriented, with a Glasgow Coma Scale of 15. He was then admitted to Neurosurgery ward with stability of clinical and neuroradiological findings for three days.

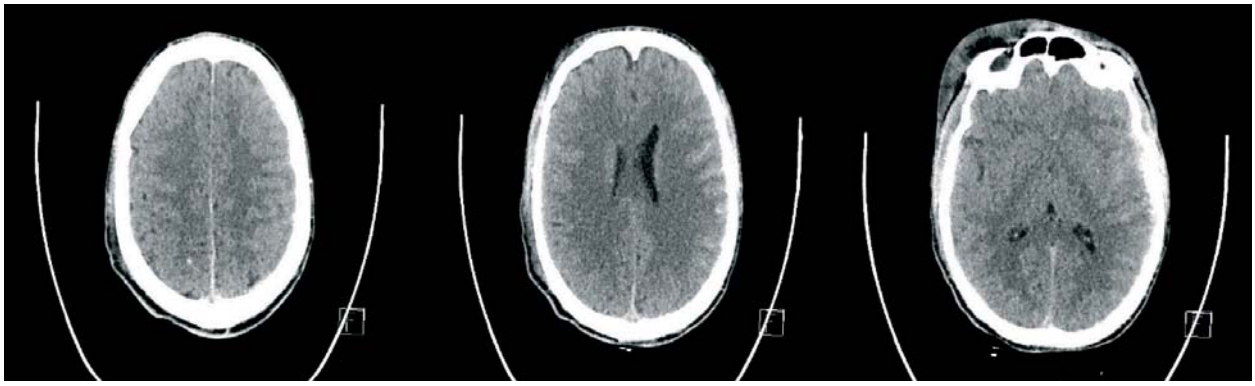

Figure 2. First axial head CT scan performed in Emergency Department showing thin striae of bilateral subarachnoid hemorrhage, a slight subdural hematoma, hemorrhagic petechia and several bones fractures.

After this period, together with pyrexia of 40 °C, his neurological condition deteriorated until a status of coma, with a drop in Glasgow Coma Scale to score 3. He exhibited no response to painful stimuli, he had fixed and dilated pupils and was not breathing spontaneously. Transferred to Intensive Care Unit he was intubated and ventilated. He performed a head MR imaging, which revealed several contusive injuries, a subtle left subdural hematoma in temporal and frontal regions and posttraumatic subarachnoid hemorrhage (*Figure 3*). Electroencephalographic findings were negative for epileptiform signs. He moreover underwent a lumbar puncture with no pathological results. His neurological conditions remained severe, with Glasgow Coma Scale score improving from 3 to 5 and evidence of right hemiplegia. A CT scan revealed reduction of both contusive lesions and subarachnoid hemorrhage, while a new head MRI, performed nine days after the previous one, showed a diffuse axonal damage (*Figure 4*).

He underwent several antibiotic therapies with reduction of inflammatory indexes, resolution of left basal pneumonia and systemic infection from Staphylococcus Epidermidis. Along with the disappearance of fever he became alert, able to understand and execute simple orders, with expressive aphasia and right arm hemiparesis.

He was then transferred to Stroke Unit. From his family history emerged the presence of two different point mutation in CACNA1A gene causing FHM in her sister and Episodic Ataxia type II (EA-2) in her mother. The patient had never experienced neurological symptoms in his life before that evening, and his genetic screening revealed a heterozygosity for a mutation in CACNA1A gene.

□ DISCUSSION

From a review of the scientific literature, we found that trauma-triggered "delayed cerebral edema" can thus be added to the wide spectrum of episodic and chronic progressive neurological disorders associated with CACNA1A mutations[14]. Kors et al. described the novel S218L missense mutation in the CACNA1A calcium channel subunit gene (*Figure 1*) in three subjects with minor head trauma-triggered delayed severe cerebral edema and coma. Two subjects belonged to a family with symptoms at the very extreme end of FHM. The third subject was the previously completely symptomatic daughter of a sporadic patient with hemiplegic migraine. She had never experienced migraine or hemiplegic phenomena before. They hypothesize that the S218L CACNA1A mutation renders subjects at risk for a disinhibited cytotoxic edematous response to minor brain injury, mediated through dysfunction of neuronal voltage-dependent P/Q-type calcium channels. So one might consider advising subjects with a positive family history for hemiplegic migraine or with demonstrated CACNA1A mutations to avoid sports in which head injury is common, such as contact sports[14].

Screening for other mutations in the mutation analysis of the CACNA1A gene in our patient might be interesting.

Several pathophysiological mechanisms have been implicated in post-traumatic hemispheric swelling due to cytotoxic edema, including Traumatic Depolarization (TD)[2]. In TD, depolarization of the neuronal cell membrane potential and activation of voltage-dependent ion channels are triggered by mechanical strain on the brain. This depolarization re-

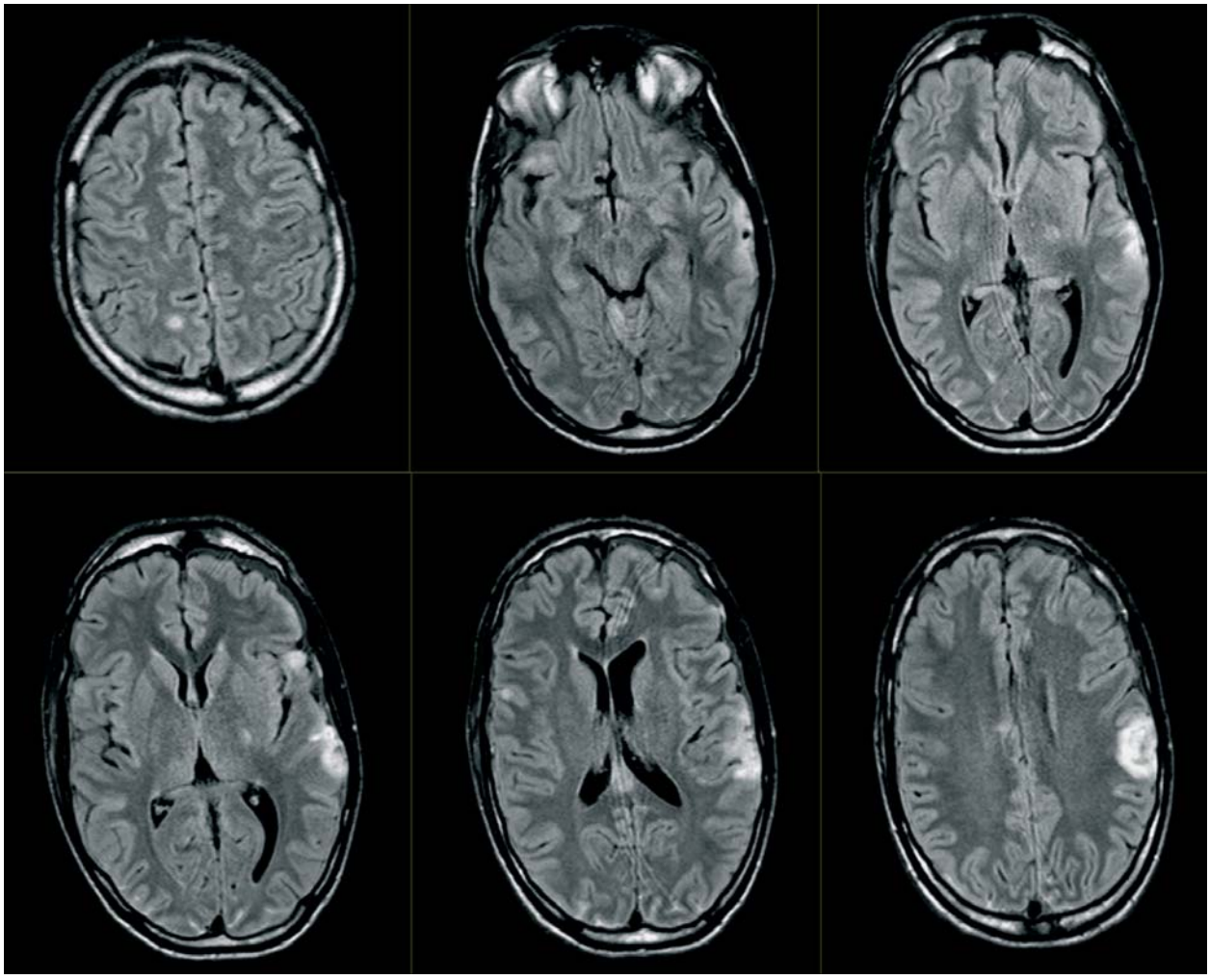

Figure 3. T2 axial brain MRI performed four days after admission, which revealed several contusive injuries, a subtle left subdural hematoma in temporal and frontal regions and posttraumatic subarachnoid hemorrhage.

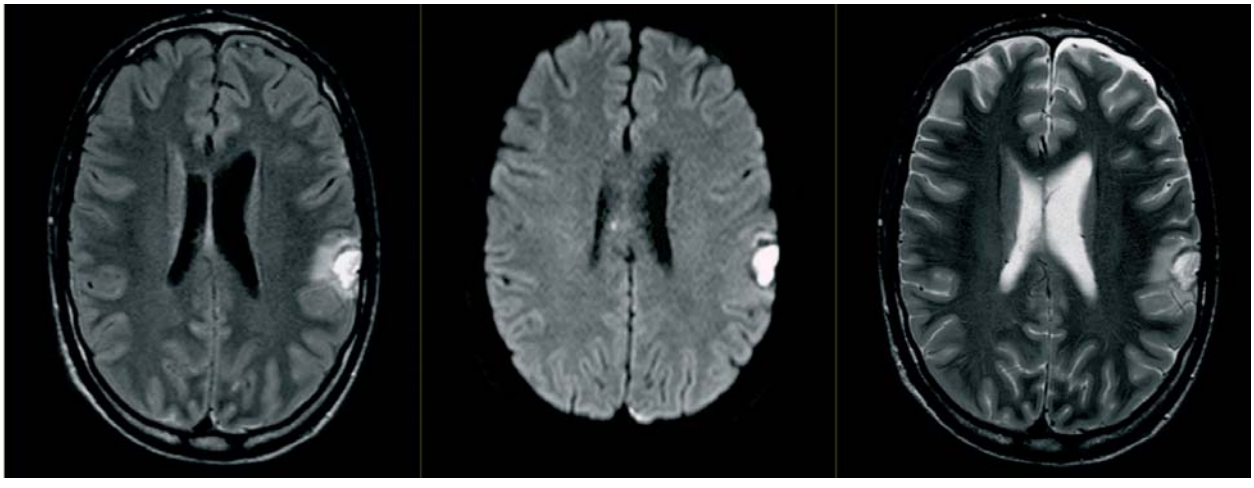

Figure 4. From left to right: axial T2, DWI and FLAIR sequences of brain MRI performed nine days after the previous one, which showed reduction of both contusive lesions and subarachnoid hemorrhage and diffuse axonal damage.

sults in massive ionic fluxes across the plasma membrane and calcium-dependent exocytotoxic release of excitatory neurotransmitters, such as glutamate and aspartate, further reinforcing the ionic perturbation and eventually causing cellular swelling[12]. The ionic perturbation, the shift of the cell membrane potential, and the pivotal role of excitatory amino acid release and K1 in TD[12] are also important mechanisms involved in cortical spreading depression. CSD is believed to be the underlying mechanism of the aura in migraine and FHM[16]. This view is supported by a recent observation that the N-methyl-D-aspartate antagonist ketamine reduced the neurologic deficits in some FHM patients[13]. So we may suppose that, if our patient had taken ketamine at that party, he could have been protected from the early cerebral damage and we can explain his absence of neurological deficits in acute phase.

The CACNA1A gene encodes for the main, ion-conducting, pore-forming a1A subunit of voltage-dependent P/Q-type neuronal calcium channels[19], which modulate neurotransmitter release[20]. Like all other known CACNA1A mutations causing FHM, the S218L mutation is a missense mutation; an amino acid change at this position would severely affect the function of the channel[14]. As a result of the S218L mutation, even weak and otherwise harmless stimuli may readily depolarise mutated Cav2.1 Ca^{2+} channels and trigger multiple and prolonged waves of CSD that are associated with severe and protracted cytotoxic cerebral edema and cell loss[14]. Enhanced release of glutamate will increase the activation of N-Methyl-D-Aspartate (NMDA) receptors, further affecting brain cells and further worsening cell swelling. Trivial head trauma may also cause mechanical strain through transient mitochondrial dysfunction and delayed long lasting small neuronal depolarisations, thereby increasing neuronal vulnerability[1]. If a calcium channelopathy is indeed an underlying mechanism in "delayed cerebral edema," treatment with acetazolamide might prove effective[14].

In conclusion, the novel S218L mutation in the P/Q-type neuronal calcium channel α1A subunit gene CACNA1A and possibly other similar CACNA1A mutations are involved in a delayed disinhibited, sometimes even fatal, cytotoxic cerebral edematous response to minor head trauma after a lucid interval. This finding could offer new avenues for the understanding and treatment of this dramatic syndrome[14].

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Case report CASI CLINICI LIBERI

□ Stroke mimics: not usual suspects

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SUMMARY: *A significant proportion of patients with acute neurological deficits, considered as stroke clinical event, mimic other pathological diseases. Ischemic stroke confirmed diagnosis is supported by neuroimaging (computerized tomography or magnetic resonance) performed 24-48 hours after clinical event. In last years, studies conducted in Stroke Centres, revealed that 25-38% of patients examined by stroke team experts had no cerebrovascular problem. Transient ischemic attacks, migraine with aura, brain tumors, seizure, hypoglycemia and functional disorder represent common stroke mimics presentations. Despite a good safety of intravenous thrombolysis in patients who have stroke-mimics, an early diagnosis of alternative cause of sudden-onset neurological symptoms consents to avoid an inappropriate use of stroke facilities and treatment. Modern neuroimaging use in Emergency helps identifying stroke mimics. A brain magnetic resonance at baseline could improve diagnostic accuracy and lead clinicians to a proper therapy. This article describes a sudden-onset of neurological symptoms related to a rare neurodegenerative disorder. In acute phase, medical history suggested a rapid symptoms appearance within few days. Ataxia on neurological examination and computerized tomography brain scan were confounding elements for the correct diagnosis. In the wide range of neurodegenerative disorders, in comparison with Alzheimer's or Lewy Body's or Parkinson disease, sporadic Creutzfeldt-Jacob disease comprises a large spectrum of clinical-pathological variants with heterogeneity in symptoms and signs, disease duration, electroencephalogram trace, size and location of brain lesions. Aim of this case report is increase clinicians awareness that uncommon stroke alternative diagnosis may include sporadic Creutzfeldt-Jacob disease as already described in literature.*

KEY WORDS: *Neurodegenerative disorder, Sporadic Creutzfeldt-Jacob disease, Stroke-mimics.*

□ CASE REPORT

In May 2019, a 67 year-old man was admitted in our Emergency Department for sudden-onset of postural instability and an acute change in cognition. The patient had a medical history of arterial hypertension and dyslipidemia well treated. He was a lifelong non-smoker and did not drink alcohol. On examination he was afebrile and his vital signs were stable. The neurological examination revealed no problem in speech fluency and comprehension with some spatial and temporal orientation mistake and miscalculation. On walking, he felt "unstable" with a marked ataxia in absence of apparent unilateral motor or sensitivity deficits. At that time, a non-contrast Computed Tomography (CT) scan revealed a right cerebellar hypodensities suspected for vertebra-basilar ischemic lesion without stenosis or occlusion on CT-angiogram. No intravenous thrombolysis was performed for 4 days persistence of symptoms. In few days, he

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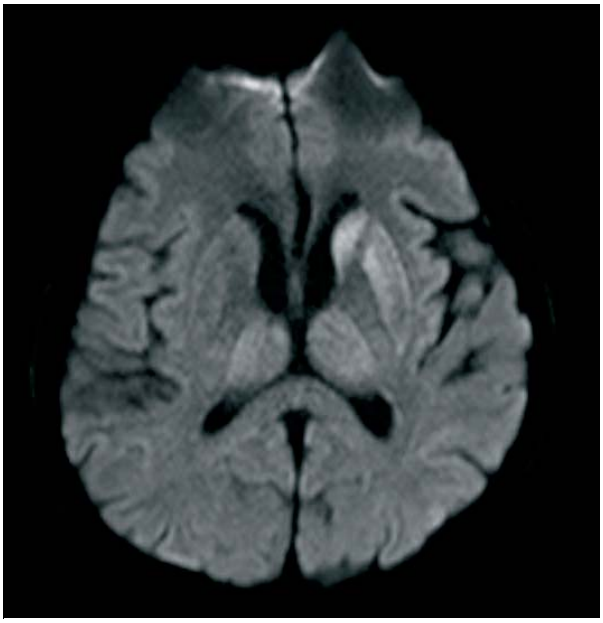

Figure 1. DWI-MRI sequence showing bilateral thalamus and left caudate nucleus and putamen restriction.

rapidly developed slow speech, dysarthria, labile affect, bilateral tremor and right arms rigidity, but he was able to walk with a single support. At first investigations, no substantial basic blood test alterations were detected including electrolytes abnormalities, B/D/E or other vitamin's deficiencies, autoimmune workup or infectious serology (Human Immunodeficiency Virus: HIV-included). Brain Magnetic Resonance Imaging (MRI) was performed four day after admission and excluded the presence of right cerebellar ischemic lesion. Unexpected images on MRI included Diffusion-Weighted (DW) bilateral thalamus and left caudate nucleus and putamen restriction (*Figure 1*). CerebrosSpinal Fluid (CSF) labs confirmed no signs of infection, malignant or autoimmune disease. West-Nile was negative. Despite an ElectroEncephaloGram (EEG) not significant for encephalopathy, patient's neurological picture enriched with visual allucinations, comprehension difficulty and dysphagia with some march difficulty with walker. Repeated MRI showed no progression of focal lesions, but remarkable stable alterations on DWI. After one month of hospitalization, the patient had myoclonus, rigidity progression also affecting left arms and neck and finally akinetic mutism. The patient expired 53 days after hospital admission. Clinical picture, MRI alterations and CSF assays were helpful to suggest a probable sporadic Creutzfeldt-Jakob Diseases (sCJD) diagnosis. Characteristic features of spongiform encephalopathy may be detected by autopsy (in progress).

□ DISCUSSION

Being aware of stroke-mimics is fundamental to consent other tractable disease early diagnosis and to reduce the use of inadequate expensive facilities and treatment including IntraVenous thrombolysis (IVT). Sudden-onset of neurological symptoms and focal lesion on CT scan were confounding elements in the reported case. Based on stroke mimics literature[1-6], unusual presentation syndrome includes not sudden neurological involvement, "positive" symptoms like movement disorders, paresthesia or seizure and detection of brain lesion not related to clinical signs[2]. Atypical presentation of sCDJ may include ataxia, thalamic presentations or visual disturbance that might be mistaken as a stroke[7]. Patient with CJD become clinical similar over time with a final phase of akinetic mutism before death[7]. When stroke diagnosis is performed two-three days after clinical event, medical history of patient including environmental context and familiar/genetic predisposition may lead to unusual diagnostic hypothesis such as feed poisoning, carbon monoxide intoxication, deficiency vitamin disease as well as neurodegeneration disease like Huntington Korea or Alzheimer disease or genetic association with familial hemiplegic migraine. Neurodegenerative disorders represent about 2-5% of stroke mimics[3,4]. In acute phase, biochemistry and CSF can exclude infections, electrolytes alterations, vitamin deficiency. Neuroimaging plays a main role in detection of stroke mimic, in particular use of MRI decreases the risk of mimics. Brain MRI abnormalities may be located in the caudate/putamen nucleus and/or in the cortex and detected as ribboning images in diffusion weighted imaging or Fluid-Attenuated Inversion Recovery (FLAIR)[8,9]. Rudge et al. compare radiological findings in sCJD and Creutzfeldt-Jakob Diseases (CJD)-mimics such as Alzheimer, Lewy body disease, immune-mediate encephalopathy, lymphoma, progressive multifocal leukoencephalophathy. Atrophy was usually generalized in CJD than in controls (CDJ mimics), but the most stricking difference between two groups was on diffusion weighted sequences: 92% of CJD showed DWI restriction especially in basal ganglia and/or cortex, 19% of all sCJD had diffusion restriction in

DEFINITE sCJD
Progressive neurological syndrome AND neurophatologically or immunocytochemically or biochemically confirmed
PROBABLE sCJD
I + two of II + Typical EEG [*generalized periodic complexes*]
OR
I + two of II + typical MRI [high signal in caudate/putamen or at least in two cortical regions (temporal, parietal, occipital) either on DWI or FLAIR]
OR
I + two of II + positive 14-3-3 CSF assay
OR
Progressive neurological syndrome + positive prion RT-QuIC in CSF or other tissue
POSSIBLE sCJD
I + two of II + duration < 2 years
I. rapidly progressive cognitive impairment
II. (A) myoclonus (B) visual or cerebellar problems, (C) pyramidal or extrapyramidal features (D) akinetic mutism

Table 1. Updated sCJD Diagnostic Criteria (*January 2017*).

two or more area in the cortex and no gadolinium enhancement. MRI alterations preceding neurological first symptoms in CJD proven autopsy patient is reported[9]. Although MRI abnormalities are commonly observed in other neurological conditions, such as ischemic lesions and status epilepticus, the relevance of DWI in early clinical stages is fully supported[9,10]. In Emergency Stroke decisional route, use of MRI markedly decreases stroke-mimics[2]. EEG periodic complexes alterations usually appear in last phases, but EEG pattern not always discriminate CJD as in the reported case[8]. CSF assays could show a rarely relevant pleocytosis and confirm 14.3.3 presence. 14.3.3 protein positive is a specific finding, but its presence is described in other neurological disease such as autoimmune encephalopathy or brain neoplasm[8]. This case report emphasizes the importance of considering further investigations, especially MRI, when unusual presentation of stroke-like symptoms is reported or a lesion on CT scan is not related to neurological signs. EEG and CSF assays are also required to support CJD diagnosis based on updated 2017 diagnostic criteria (*Table 1*)[10-13].

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Case report CASI CLINICI LIBERI

□ A troubled history of chronic facial pain: case report

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SUMMARY: *A paradigmatic case of chronic facial pain will be described in which a painstaking diagnostic and therapeutic pathway submitted the patient to various invasive and non-invasive unsuccessful treatments, and only 8 years after the onset of the pain syndrome eventually was cured. Differential diagnostic pitfalls will be discussed and contact point headache will be stressed as a possible cause of disabling facial pain, which should be taken into account among other, more common, diagnoses.*

KEY WORDS: *Chronic facial pain, Cluster headache, Contact point headache, Trigeminal neuralgia.*

□ INTRODUCTION

Chronic facial pain is a major diagnostic challenge. A recent study of 101 patients with orofacial pain showed that they attended a mean of seven health care settings, seen a mean of three specialists and only 24% eventually had a satisfactory treatment[3]. Up to 48% had been misdiagnosed by the primary care physicians[24]. A wrong diagnostic classification of these patients is thus frequent and may conduct to a wrong care pathway and inadequate treatments, often influenced by the background of the specialist assessing the patient[15].

The precise collection of historical data and the careful description of the main characters of the pain syndrome are crucial for a correct clinical diagnosis, as objective radiological and/or laboratory data may be lacking[20]. Trigeminal neuralgia, cluster headache, temporomandibular joint pain and muscle disorder-type pain are common types of non-odontogenic pain in population based studies among adults[10]. Nevertheless, still many patients, for instance with trigeminal neuralgia, are submitted to multiple dental avulsions before a correct diagnosis is made. Functional disorders associated to depression and anxiety must also be excluded by psychological assessments[15], keeping nevertheless in mind that chronic pain itself is a cause of emotional distress and disability. This is particularly true whenever subjective symptoms are not substantiated by cogent objective clinical and/or radiological data.

We present a unique and paradigmatic case of chronic invalidating facial pain in which, as a result of repeated misdiagnoses, the patient was submitted to multiple invasive and non-invasive treatments without effect. The correct diagnosis and a simple surgical procedure eventually solved the case.

□ CASE HISTORY

This 52 years old male with a history of arterial hypertension has been admitted in 2016 to the Department of Neurosciences of the San Gerardo Hospital of Monza for the persistence of a severe disabling facial pain, unresponsive to previous pharmacological

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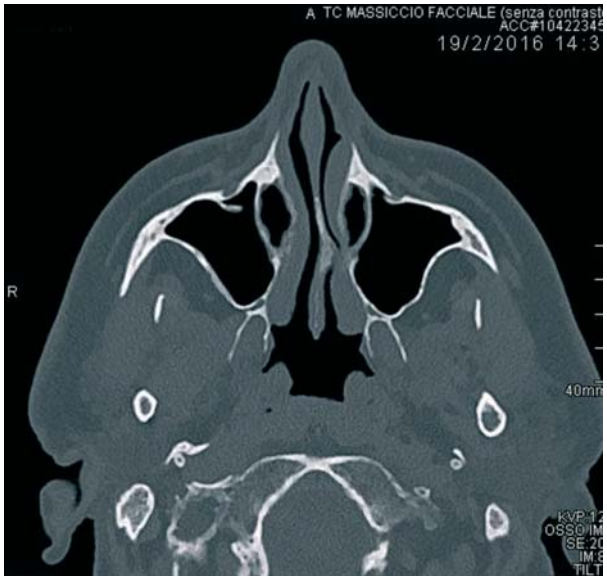

Figure 1. Axial CT showing left spur in contact with the inferior turbinate.

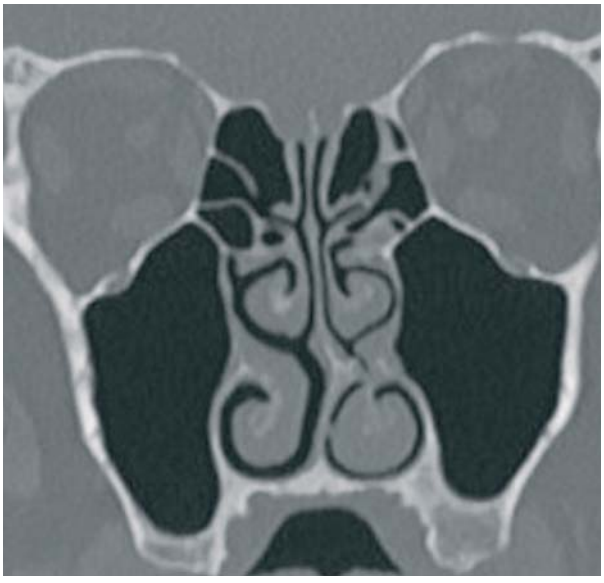

Figure 2. Coronal CT showing left deviated septum and septal spur in contact with the inferior turbinate.

and surgical treatments. Left neuralgic pain, starting 8 years earlier, was characterized by repeated daily attacks of paroxystic sharp and lightening pain referred to the first and second branches of the trigeminal nerve (V1,V2), followed by dull ache. At that time a diagnosis of "atypical trigeminal neuralgia" was made. The patient was treated with growing doses of Carbamazepine (CBZ) and Gabapentin (GABA) without pain control. One year later an MR imaging study evidenced a possible left neurovascular conflict between the anteroinferior cerebellar artery and the trigeminal nerve at the root entry zone, without clearcut evidence of nerve dislocation or impression. Due to the persistence of neuralgic pain, notwithstanding high doses of CBZ and GABA, the patient was submitted to microsurgical decompression of the fifth cranial nerve two years later, without any clinical improvement. Many further drug treatments were attempted but none of them was able to control the invalidating pain, with the exception of intravenous steroids during the most severe pain attacks. Three years later, the patient was evaluated by a functional neurosurgeon and a palliative treatment with invasive motor cortex stimulation was proposed and carried out. Also this procedure resulted fruitless. Botox injection of facial muscles was thereafter prescribed without any pain control. A neurological re-evaluation reconsidered the initial diagnosis, suggesting that this patient could be affected by "atypical cluster headache" and increasing doses of verapamil and oxygen therapy during paroxysms were prescribed. Also these treatments resulted unsuccessful. At admission in our Department, 8 years after the onset of the pain syndrome, a thorough clinical re-evaluation of the case history, the characteristics of the painful neuralgic bouts, their topography, the presence or not of accompanying autonomic features and/or photophobia, the presence of trigger zones or aggravating factors, the response to previous treatments, was made. Previous diagnoses were rejected for the absence of typical symptoms and signs and the futility of all attempted therapies. A thorough psychological evaluation and tests didn't evidence significant psychiatric problems, thus excluding a functional, psychosomatic, etiology of the pain syndrome. According to the neuralgic aspects of the pain, its localization in the periorbital and maxillary area of the face and the absence of the main typical characteristics of the more common chronic, non dental, orofacial pains, a tentative diagnosis of ethmoidal contact neuralgia was made and a detailed CT study of the bony face requested. Coronal CT slices of the nasal cavity clearly evidenced a left deviated nasal septum and a septal spur with mucosal contact (*Figure 1* e *2*). A contact point headache was thus presumed. Positive xylocaine plus adrenaline test supported the clinico-radiological diagnosis by temporary relief of the facial pain. The patient was thus referred to the otorhi-

nolaryngologist who carried out septoplasty, removal of the septal spur and decongestion of the turbinate. After the procedure, for the first time after 8 years, the patient was relieved by his disabling neuralgia with only minor persisting aches. The satisfactory clinical result is still present after a three-years follow-up and the patient only occasionally recurs to analgesic drugs and declares that the only useful treatment has been the othorhinolaringological procedure.

□ DISCUSSION

Chronic facial pain can still be an intriguing clinical challenge and patients are often submitted to painstaking diagnostic journeys with multiple diagnoses and various therapeutic proposals, often influenced by the clinical background of the specialist assessing them. Current diagnoses include tension headache, trigeminal neuralgia, migraine, cluster headache, temporomandibular joint disorders, and so called chronic or atypical facial pain. In most cases the patient's subjective pain experience is not related to objective changes and only the most accurate and critical evaluation of patient's narrative, compared to well known clinical syndromes, can afford a correct diagnosis which should be thereafter confirmed by the efficacy of selected drug treatments (ex juvantibus).

The present patient can be considered as a paradigm of the traps in which patients can incur because of a superficial or forced initial clinical diagnosis. At the first referral, the patient was classified as affected by atypical Trigeminal Neuralgia (TN). Indeed, his clinical picture apparently fitted with the definition of TN provided by the International Classification of Headache Disorders (ICHD-3)[10]: repeated unilateral paroxysmal attacks of intense, shock-like pain along one or more trigeminal divisions, associated, in the atypical form, with persistent pain in the affected area. There are, however, some clinical and imaging features, in our case, that should have raised the suspicion of an alternative diagnosis. One of such features is the lack of typical trigger points, which is reported in only 1% of patients with primary TN[13]. An algorithm for a graded diagnosis of trigeminal-based pain has been proposed[8], indicating the presence of a triggering effect of innocuous stimuli or manoeuvres as the key element that elevates the level of diagnostic accuracy *from possible to probable* TN. Triggered pain is in fact a somatosensory phenomenon unique to neuropathic conditions[18], hence its high diagnostic value for primary trigeminal disorders. A second feature is the lack of objective nerve structural abnormalities in association with the neurovascular conflict subsumed on MR imaging. Crucially, algorithm-based diagnosis of probable classical TN requires the presence of neurovascuar compression with morphologic changes the trigeminal root. A proportion of totally asymptomatic trigeminal nerves ranging from 17% to 36% show a nerve-artery contact on MR imaging[1,2,9]. MR images should be acquired and scrutinized specifically for nerve dislocation or atrophy, which are deemed to be the actual determinants of neuropathic trigeminal pain[12,14]. Finally, two other features of our patient are not strict indices of symptomatic TN per se, but their co-occurrence, especially within a diagnosis of possible, rather than probable, TN should have prompted investigations above and beyond routine diagnostic workup for facial pain: involvement of the area of the first trigeminal branch and the poor response to pharmacological and surgical treatments. Ophtalmic involvement has no clear-cut association with an increased risk of secondary TN, but is uncommon, having been shown in only 5% of cases of primary TN[5], and surely is less typical of classical TN than the combination of the other two divisions[8,10]. Standard therapies may not be fully beneficial, in particular in patients with atypical TN[10], but satisfactory relief is achieved in approximately 90% of patients, even only by first-line medications[7,9], to the point that a positive response to CBZ or oxCBZ is proposed as an operant diagnostic criterion on TN[8].

The second tentative diagnosis suggested for the patient, years after the first diagnosis, was atypical cronic Cluster Headache (cCH) and was mainly based on the temporal characteristics of pain attacks, which, at that point, had a longer duration and tended to occur in an apparently cyclical pattern during the day and overnight. Furthermore conjunctival injection, that was occasionally evident during the attacks, was also considered supportive of the diagnosis. IHCD-3 criteria for cCH require severe unilateral periorbital headache plus at least one symptom/sign of autonomic dysfunction, presenting in characteristic temporal clusters, and with maximum 30 days of remission per year[10]. Unusual features like unremitting pain between clusters, or particularly rare attacks qualify the symptomatology as atypical[21]. Slavish application of these criteria did lead to a diagnosis of atypical CH in our patient. More careful considera-

tion of history and neurological signs and symptoms, though, reveal some aspects that make the diagnosis questionable. In disagreement with the literature, which has established a 97% prevalence of dysautonomic symptoms in CH[16], in our case there was only mild and occasional conjunctival injection.A symptom which may, besides, be quite aspecific, since minor manifestations such as lacrimation or eye redness may accompany many forms of facial pain or headache as part of the trigeminovascular reflex[10,16]. Timing of attacks was atypical, and is not always easy to establish precisely. For this reason it should not be relied upon as key diagnostic criterion, when other typical features are missing. Lastly, although irradiation to the maxillary area is reported in CH, pain is definitely more commonly localized within or above the orbit[11,16].

Contact Point Headache (CPH), also called Ethmoidal Neuralgia (EN) or rhynologic headache[6,17,19,22], is seldom considered by neurologists or neurosurgeons involved in pain ore headache clinics. Still many specialists don't believe in this nosological entity and potential favourable effects of rhynological surgery and the clinical diagnosis of CPH remains controversial. Shalom already described the anterior ethmoidal nerve syndrome in 1963[22]. Morgenstein and Krieger[17] described middle turbinate headache syndrome, caused by vasoactive engorged middle turbinate that compresses against a deviated nasal septum. In 1988 Stammberger and Wolf[23] explained the cause of rhynogenic headache as a mechanical contact between two mucosal surfaces creating a sensory stimulus resulting in release of substance P responsible for migraine-like symptoms. In 2005 an extensive review on craniofacial pain and anatomical abnormalities of the nasal cavities has been published, ponting on the physiopathological and anatomical aspects of the disease[6]. More recently Behin and Rai published their encouraging surgical results[4,19]. On the basis of published data we thus believe that also CPH should be considered in the workup of patients presenting with chronic facial pain unfitting with the more common and well described differential diagnoses, avoiding an ill advised diagnosis of atypical or idiopathic pain syndrome. Ethmoid neuralgia, secondary to mucosal contact points in the nasal cavity, is usually characterized by neuralgic pain referred to the frontal, periorbital, infraorbital, nasal or malar region of the face, both unilateral (more common) or bilateral[19]. Attacks of stabbing and lancinating pain can present 5-8 times/ month and in some patients, as ours, can have more than one daily attack and become severely disabled. Once the more common diagnoses are excluded a coronal CT scan and nasal endoscopy can visualize anatomical variations of nasal cavities such as septum deviations and bony spurs impinging on nasal mucosa and ethmoidal nerve branches. Xylocaine-adrenaline test is then used to confirm their possible physiopathological role. Once the current pain is temporarily relieved, the test is considered positive and, in the opinion of many authors, represents a good indication to surgery.

□ CONCLUSIONS

To attain the correct diagnosis in chronic facial pain syndromes is often a difficult task as in the majority of the patients no objective clinical or laboratory signs can definitely substantiate clinical suspects. The critical recollection of subjective symptoms is crucial and has to be compared with the well known and well described common pain syndromes. Whenever symptoms and signs don't precisely fit diagnostic algorithms, one should avoid to rapidly classify the patient as atypical and further possible diagnoses should be considered. Among them contact point headache deserves, in our opinion, attention and should be always considered, as a simple rhynological procedure could cure the patient.

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Abstract CASI CLINICI LIBERI

□ Meninges: a multidisciplinary interest

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Aims. Rheumatoid meningitis is a rare complication of rheumatoid arthritis. It is associated with substantial morbidity and mortality. The condition may be present in a variety of ways and it is therefore diagnostically challenging. Uncertainty still exists regarding the optimal treatment strategy.

Materials and Methods. We describe the case of a 50-year-old woman with a recent history of metatarsal arthritis. The patient came to Emergency Department for a first episode of tonic-clonic seizure. Magnetic Resonance (MR) imaging revealed an iperintensity Fluid-Attenuated Inversion Recovery (FLAIR) signal at frontal bilateral cortex with prevalence on left side and a subtle enhancement of the falx and at the surface of bilateral frontal cortical convexity. Cerebrospinal fluid analysis revealed a leukocyte pleocytosis but normal proteins and glucose, normal immunophenotype, negative research for cancer cells and Koch bacillus. A total body computerized axial tomography did not reveal evidence of an underlying malignancy. The patient experienced other seizures, which required a specific antiepileptic treatment; furthermore, the patient presented diffuse arthalgias and MR control showed an extension of the pathological involvement of left frontal hemisphere. Therefore, a corticosteroid therapy consisting in methylprednisolone 1,000 mg IV daily for 5 days, and then prednisone (1 mg/kg) was administered. Clinical rheumatological evaluation and laboratory analysis lead to a first diagnosis of psoriatic artropathy and then to a definite rheumatoid arthritis. An open meningeal biopsy was performed for the confirmation of the diagnosis before starting immunosuppressive therapy.

Results. Histopathologic analysis of the meningeal biopsy revealed a chronic granulomatous inflammation with focal areas of necrosis. The inflammatory infiltrate consisted primarily in CD68 positive macrophages, plasma-cells and some giant cells. These pathologic findings were consistent with the diagnosis of rheumatoid arthritis.

Conclusions. This is a case of rheumatoid meningitis presenting with convulsive seizures. The neurological presentation has anticipated the rheumatological diagnosis. The correct management of this entity is difficult, the final diagnosis can be made only based on the results of histological analysis. Different immunological therapies can be proposed to the patient.

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Abstract CASI CLINICI LIBERI

□ A 60-years-old woman with acute dystonia and tetraparesis

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A 60-year-old woman with paroxysmal atrial fibrillation treated with percutaneous left atrial appendage occlusion presented with sudden-onset tetraparesis.
Neurological examination showed left lower facial palsy, symmetric hypertonic paraplegia and left upper limb weakness. Stereotypies and dystonic posture of the right upper limb as well as left-sided hemianesthesia were also observed.
Blood examination, EKG, toxicology screening and brain CT scan were unremarkable. CT angiography demonstrated bilateral anterior and distal right middle cerebral arteries occlusion, confirmed by CT perfusion and MRI scan.
Right-sided symptoms resolved within 24 hour. Transoesophageal echocardiography ruled out Watchman device displacement. Oral anticoagulation therapy was started.

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Abstract CASI CLINICI LIBERI

□ Drug resistant hiccups and neuromyelitis optica spectrum disorders

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We report the case of a 35-year-old Chinese man that, one month after previous poorly steroid responsive optic neuritis, developed a discomforting persistent hiccup. All gastrointestinal investigations were unremarkable. Brain MR imaging showed a hyperintense T2 lesion within the periacqueductalis area beside cervical cord enhancement. Considering the lesions atypical for multiple sclerosis, also anti-Myelin Oligodendrocyte Glycoprotein (anti-MOG) and anti-NeuroMyelitis Optic (anti-NMO) assay were obtained. The latter dosage positive, taken together with neuroradiological investigations, highlights the diagnosis of NeuroMyelitis Optica Spectrum Disorder (NMOSD). Due to partial responsiveness with metilprednisolon, PLasma EXchange (PLEX) and Intra-Venous Immunoglobulin (IVIg), Rituximab was introduced, with complete control of clinical and radiological disease activity.

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Atti a cura di Elio Clemente Agostoni, Andrea Salmaggi, Domenico Consoli, Bruno Zanotti

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Abstract CASI CLINICI LIBERI

□ Incomplete Pourfour du Petit Syndrome: a clinical case

M. GIUNTA, A. PEZZINI, L. POLI, S. COTTI PICCINELLI,
M. CORTINOVIS, F. SCHIANO DI COLA, A. PADOVANI

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Introduction. Pourfour du Petit Syndrome is characterized by an autonomic disfunction consisting of unilateral mydriasis, eyelid retraction and hyperhidrosis. We reported a case lacking the last two symptoms.

Case report. A 39 years old Caucasian man, with no relevant medical history, was conducted to the emergency department due to anisocoria, associated with cervical pain abrupted two days before. Neurological examination was unremarkable, except for anisocoria with left eye mydriasis. Brain computed tomography scan performed at admission showed no densitometric abnormalities. In order to exclude a parasympathetic dysfunction a diluite/not-diluite pilocarpine test was conducted, which produced, respectively, no constriction and only a minimal pupillary constriction, excluding an iatrogenic effect. Brain MR imaging with study of the intracranial arteries documented no parenchymal or vascular alterations. In particular, a cervical artery dissection was excluded. On day three, the patient developed a vesicular rash on the neck, without a clear trigeminal involvement. No sign of acute HSV infection was found. An incomplete Pourfour du Petit Syndrome was diagnosed.

Discussion. Though Poufour du Petit and Bernard-Horner Syndromes share the same system involvement, the former proceeds an irritating lesion from different etiologies. A cervical ganglia involvement, secondary to neurotrophic Varicella Zoster Virus infection, could be included in the diagnostic work-up.

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Abstract CASI CLINICI LIBERI

An atypical case of sleep-related headache improved after treatment of a severe sleep breathing disorder

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Different forms of primary or secondary headaches have a relationship with sleep. For instance, headache represents a common symptom reported by patients with Sleep Breathing Disordered (SDB) and tends to occur typically at awakening. Thus, accordingly with the International Classification of Headache Disorders (ICHD 3b), the "sleep apnea headache" is defined as morning headache of less than four hours' duration caused by sleep apnea. Conversely, Hypnic Headache (HH) represents a rare primary headache disorder, characterized by strictly sleep related headache attacks. The pathophysiology of HH is still enigmatic and the role of SDB is highly debated.

We reported the case of a 57- year old woman affected by metabolic syndrome and migraine without aura that developed a medication-overuse headache for which she was submitted to a structured withdrawal hospitalization in 2014. After discharge, therapy with pizotifen and duloxetine conducted to a significant reduction of the episodes frequency (< 1/month) for about 3 years. In 2017 a further hospitalization occurred because of the abrupt onset of several nocturnal headache attacks, awakening the patient. They occurred every night, usually after 2-3 hours from sleep onset. The headache was described as diffuse, pulsating, of severe intensity, and without associated nausea, photophobia, phonophobia, ptosis, lacrimation, or rhinorrhea. The headache was abolished in 5-10 minutes after assuming the upright position. Considering that patient complained also snoring and excessive daytime sleepiness, she underwent a portable sleep cardiorespiratory monitoring that revealed a severe obstructive sleep apnea associated with hypoventilation. The treatment with nasal Continuous Positive Airway Pressure (CPAP) induced an immediate and complete resolution of the sleep apnea and the headache attacks.

This represents an unusual case of a secondary form of headache with clinical features similar to those of HH, except for the shorter duration. The rapid and marked response to the CPAP therapy allows to hypothesize the role of the oxygen desaturation and probably of the consequent cerebral blood flow modifications in the genesis of this disorder.

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Abstract CASI CLINICI LIBERI

□ An unusual case of axonal neuropathy

S. COTTI PICCINELLI, B. RISI, E. BALDELLI, N. NECCHINI,
S. GALLO CASSARINO, F. CARIA, M. FILOSTO, A. PADOVANI

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Introduction. Leprosy, also called Hansen disease, is an endemic disease in many countries of the world, but almost completely eradicated in Western countries. Among the many manifestations of the disease, the bacterium can sometimes affect peripheral nerves, causing sensory-motor neuropathies.

Case report. A 34-year-old Brazilian woman complained about sensory impairment and dysesthesias at the distal segments of the four limbs since about 2 years. Neurological evaluation showed tactile and pinprick sensory impairment and vibratory and proprioceptive sensory loss in the lower limbs. ENG study showed reduction of amplitude of the Motor Action Potential (MAP) of the right common peroneal nerve and absence of the Sensory Action Potential (SAP) of both the sural nerves and right ulnar and median nerve. Immunological screening including Anti-Nuclear Antibodies (ANA), Extractable Nuclear Antigens (ENA), AntiNeutrophil Cytoplasmic Antibody (ANCA), Lupus AntiCoagulants (LAC), C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Angiotensin-Converting Enzyme (ACE), Hepatitis B surface antigen (HbsAg), anti-Hepatitis C Virus (HCV), anti-Human Immunodeficiency Virus (HIV), anti-Borrelia Burgdorferi IgM and IgG, anti-Treponema antibodies, anti-Transglutaminase antibodies, anti-Ganglioside antibodies, onconeural antibodies and anti- Myelin-Associated Glycoprotein (MAG) antibodies were unremarkable. Carcino-Embryonic Antigen (CEA), Carbohydrate Antigen 19.9 (CA 19.9), Cancer Antigen (CA) 15.3 and CA125 were negative. CerebroSpinal Fluid (CSF) analysis showed no signs of inflammation. Molecular analysis of TransRhyRetin (TTR) gene was normal. A biopsy of the right sural nerve was then performed. The study showed nerve fascicles with subverted structure with severe infiltration of inflammatory cell. Alcohol-acid resistent, Ziehl-Neelsen positive bacilli inside the nerve bundles were identified. These findings were suggestive of leprous neuropathy.

Discussion. Leprosy can be a rare cause of axonal motor neuropathy even in Western countries. Diagnosis is made through nerve biopsy. Early recognition of this condition is very important in order to start adequate antibiotic therapy as soon as possible and limit nerve damage.

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Abstract CASI CLINICI LIBERI

□ A diagnostic dilemma: neurosarcoidosis or neuro-tuberculosis?

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A 45 year old Pakistani man was sent by his G.P. to perform an ambulatory neurological visit for rapidly progressive urinary retention since one and half year needing a bladder catheter and progressive gait impairment with ataxia since six months. The patient was admitted to the Neurology Unit and a lumbar spinal cord RM was requested. As patient was found positive to the Quantiferon test and the Rx chest showed multiple nodules, a CT chest scan was performed, setting the suspect for sarcoidosis. Then, brain and full spinal cord with contrast was performed, showing enhancement of cauda equina, dorsal and cervical roots, left and right III cranial nerves and cerebellar scissures, suggesting to investigate both for neurosarcoidosis and neuro-TuBerculosis (TB). Blood and urine sample were negative for TB (microscopy and Polymerase Chain Reaction: PCR findings). A lombar puncture and a broncoscopy were performed, showing no signs of TB at the microscopy and at the PCR for Mycobacterium, limpid CSF with low glucose and high limphocytes, and granulomatous lymphadenitis at the thoracic nodes biopsy. We treated the patient both for TB and neurosarcoidosis, with a great improvement of gait and the removal of bladder catheter. After three month, TB culture on blood, urine and CerebroSpinal Fluid (CSF) were negative. Still, Neuro-Tb could not be absolutely excluded.

This case report represent a very hard neurological clinical dilemma, showing that sometimes neurologists must be ready to empirically treat a patient, even without a definitive diagnosis.

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Abstract CASI CLINICI LIBERI

□ Paraneoplastic anti-NMDA receptor encephalitis

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B. RISI, S. COTTI PICCINELLI, A. PADOVANI

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Anti N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis is an autoimmune disorder associated with antibodies against NMDA receptor, frequently occurring in patients with an underlying neoplasm, mostly ovarian teratomas. Common clinical features include neuropsychiatric signs and symptoms, like changes in behavior, psychosis, seizures, and abnormal movements.

Here we describe the case of a 47-years old man, whose clinical history was unremarkable, who experienced progressive worsening psychiatric symptoms, cognitive deficits, apathy, extrapyramidal stiffness and a tonic-clonic seizure.

Laboratory studies and brain MR imaging were negative for any acute process, EEG showed epileptiform abnormalities, and CerebroSpinal Fluid (CSF) testing revealed the presence of anti-NMDA receptor antibodies. High-dose corticosteroids were administered for five days, followed by plasma exchange. Total body CT scan revealed a minimally-invasive lepidic-growth lung adenocarcinoma, so that a diagnosis of paraneoplastic anti-NMDA receptor encephalitis was made. The tumor was surgically removed, and the patient was discharged with a mild improvement of his symptoms. Anti-NMDAR encephalitis always represents a diagnostic challenge, due to its insidious manifestations. Approximately 30-40% of patients have an associated underlying neoplasm, but no cases of minimally-invasive lepidic-growth lung adenocarcinoma have been described in literature so far.

Our case suggests that anti-NMDAR encephalitis may be associated to a large variety of tumors that need to be deeply investigated in all patients.

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Abstract CASI CLINICI LIBERI

□ Fibrous myopathy as a rare complication of drug abuse

B. RISI, S. GALLO CASSARINO, S. COTTI PICCINELLI, A. GALVAGNI, F. CARIA, E. BALDELLI, N. NECCHINI, C. BARONCHELLI, M. FILOSTO, A. PADOVANI

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Introduction. Drug-induced myopathy is a rare cause of muscle disease, ranging from mild myalgias to chronic severe weakness. Among all types, focal myopathy with associated fibrosis resulting from repeated intramuscular injections of narcotic analgesics has been sporadically described. To our knowledge, only three cases of myopathy following heroin injections have been reported to date.

Case report. We here describe a 48-year-old man with a history of intramuscular drug abuse who presented with slowly progressive asymmetric weakness and hypotrophy of the scapulohumeral girdle for about three years. A scleroderma-like skin pattern was evident especially in the forearms and thighs. Endocrine, renal and liver dysfunctions, inflammatory or rheumatic disorders, electrolyte imbalance, vitamin deficiencies, hepatitis B and Human Immunodeficiency Virus (HIV) infection were ruled out by appropriate laboratory investigations. Hepatitis C virus (HCV) positivity has been known for many years. Patient revealed intravenous and intramuscular heroin abuse. Deltoid muscle biopsy showed the presence of diffuse endomysial fibrosis, muscle fiber degeneration, adipose infiltration and widespread anti Major Histocompatibility Complex-class I (MHC-I) antibody membrane positivity. Immunohistochemical studies for Dystrophin, Alpha-sarcoglycan, Gamma-sarcoglycan, Beta-sarcoglycan, Delta-sarcoglycan, Caveolin-3, Dysferlin, Alpha-dextroglycan, Merosine, Collagen IV, Collagen VI and Telethonin were normal. Skin biopsy showed a reticular dermal thickening as per a scleroderma-like process. A next generation sequencing study for several myopathic conditions showed no pathogenic variants.

Conclusion. After excluding main inherited and acquired myopathies, the final diagnosis was a fibrous myopathy related to drug abuse.

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Abstract CASI CLINICI LIBERI

□ Subcallosal artery stroke: a clinical case

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Introduction. The fornix, a white matter bundle connecting the hippocampus to the ipsilateral mammillary body, is a core structural element of the Papez circuit. Lesions of the fornix impair both formation and consolidation of episodic memory. Infarction of the anterior fornix is characterised by significant anterograde amnesia, a rare condition known as "the amnestic syndrome of the subcallosal artery".

Case report. A 61 years old caucasian man was brought to the Emergency Department following sudden onset of anterograde amnesia, in absence of any other neurological and cognitive dysfunctions. Brain computed tomography, electroencephalography and epiaortic ultrasound were all negative. Transient global amnesia was hypothesized and the patient dismissed. Two days later, the patient was brought back due to persistence of the memory impairment and admitted to the Neurology Unit. Neuropsychological testing documented a significant verbal and visuospatial long term memory deficit. Brain Magnetic Resonance Imaging (MRI) documented bilateral isolated signal hyperintensity on diffusion-weighted imaging and hypointensity on T1-weighted image in fornix columns and anterior body, interpreted by neuroradiologists as a possible low grade glioma. Follow-up brain MRI with gadolinium revealed no sign of fornix restriction, hypointensity, contrast enhancement nor new parenchymal lesions. Given the acute onset, limited extension and imaging behaviour, a final diagnosis of acute isolated fornix ischemic stroke occlusion of the subcallosal artery - was made.

Discussion. Acute anterograde amnesia due to anterior fornix infarction is a rare condition that should be considered in the diagnostic work-up of acute amnesic syndromes. Small vessel disease of the perforating branch (subcallosal artery) is usually the most common aetiology.

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Abstract CASI CLINICI LIBERI

□ Prolonged symptomatic visual aura in posterior cerebral artery kinking

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Introduction. Arterial narrowing has been reported in migrainous infarction. Here we report a case of posterior cerebral artery kinking in a prolonged visual aura in absence of imaging signs of ischemia.
Case report. A 39 years old caucasian woman was brought to the Emergency Department due to prolonged visual aura - left temporal hemianopsia - lasting > 24 hours, accompanied by her usual migraine. Her past medical history comprised a 10-years history of episodic migraine (two/year) with visual aura, active smoking and hormonal contraceptive therapy. A significant worsening was reported within the previous weeks (4 episodes). Brain Computed Tomography (CT) and ophthalmologist evaluation were both negative. Thus, migrainous infarction was hypothesized and the patient was admitted to the Neurology Unit. Brain Magnetic Resonance Imaging (MRI) found no parenchymal lesions nor diffusion weighted imaging-restriction. MRI Angiography (MRA) documented a significant stenosis of the right Posterior Cerebral Artery (PCA), between the P1 and P2 segments. Follow-up MRA confirmed the stenosis. A further increase in aura frequency was observed, unresponsive to prophylactic treatment with low dosage aspirine, thus add-on therapy with flunarizine was introduced. Subsequent CT angiography did not confirm the stenosis, documenting instead a focal kinking.
Discussion. Arterial tortuosities hold an increased risk of microembolization and/or occlusion. Thus, in the setting of a genetically altered cerebral excitability and perfusion distinctive of migraine with aura, such anomalies might be associated with focal neurological signs, even in absence of persistent brain damage, i.e. ischemic stroke.

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Abstract CASI CLINICI LIBERI

□ Contrast-induced encephalopathy mimicking total anterior circulation stroke: a case report and review of the literature

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P. REGANATI**, A. LUNGHI**, A. RIGAMONTI*, A. SALMAGGI*

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Aims. Contrast-Induced Encephalopathy (CIE) is a rare, acute and generally reversible neurological disturbance associated with the intra-arterial administration of iodinated contrast. Risk factors seem to be hypertension and renal failure[1]. Clinical manifestations include cortical blindness, encephalopathy, seizures and focal neurological deficits.

Materials and Methods. We describe a case of a 56-years-old woman who suffered of transient hemiplegia and global aphasia after a brain angiography. She had a history of migraine, renal colic, smoking and previous heroin abuse 20 years earlier and she was hospitalized in our Department for a sulcal posterior subarachnoid haemorrhage. In order to exclude the presence of an intracranial aneurysm she performed two cerebral angiographies with the evidence of two 3 mm aneurysms at the posterior communicating artery and the anterior choroidal artery. Immediately following the second procedure she developed a global aphasia and a complete right hemiparesis.

Results. No artery occlusion or reversible vasospasm was detected on the brain MR imaging angiography, the brain CT scan revealed left cerebral oedema.

Conclusions. Patient was treated with dexamethasone and compound NaCl with a complete neurological recovery within 10 days.

Reference

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IN ESCLUSIVA

SNO CIENZE EUROLOGICHE SPEDALIERE

Eccezionale edizione italiana per tutti i cultori delle Neuroscienze:
traduzione in italiano del best seller di neuroanatomia e approcci chirurgici
di Albert L. Rhoton Jr

CRANIAL ANATOMY AND SURGICAL APPROACHES

di Albert L. Rhoton Jr

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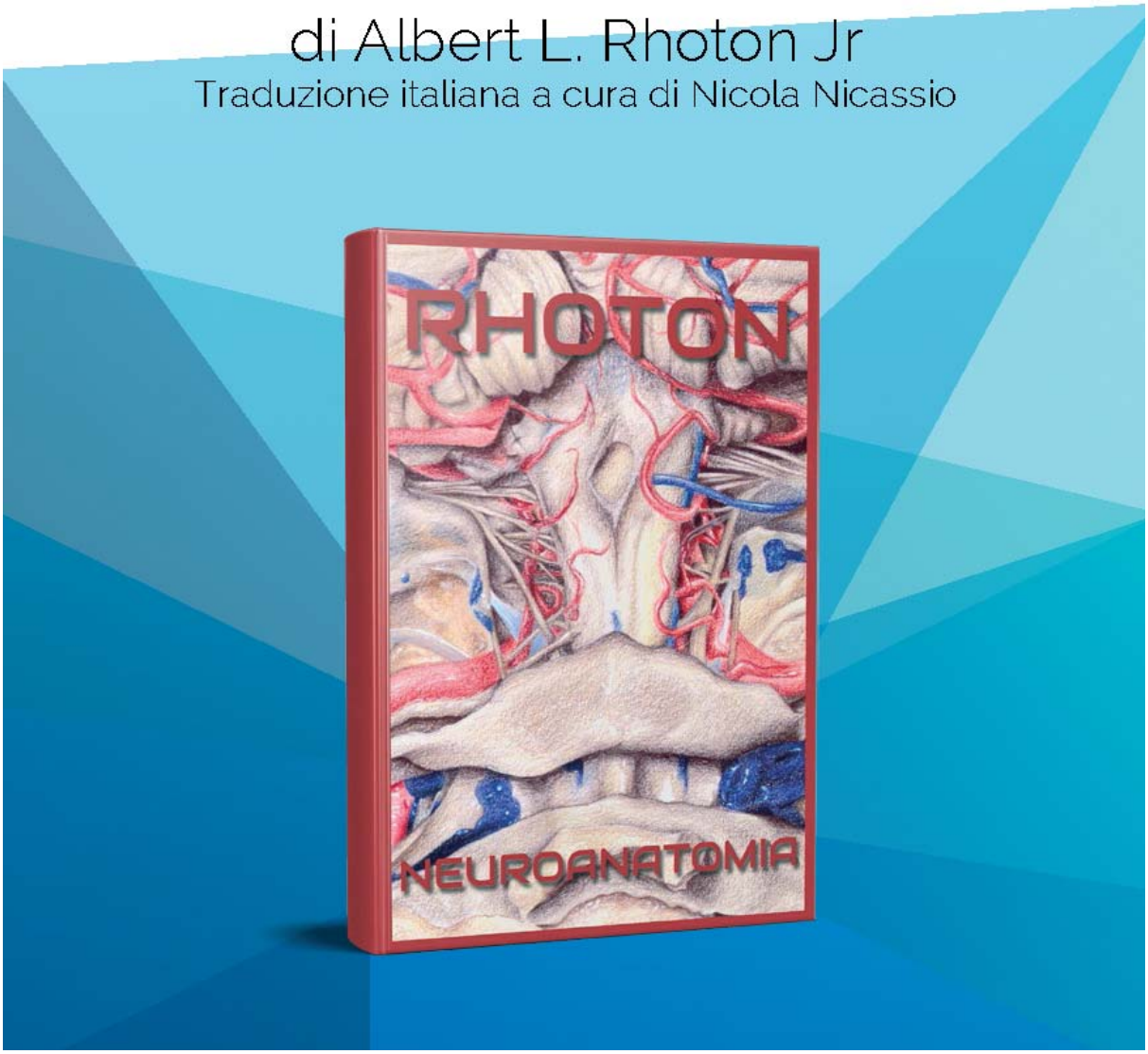

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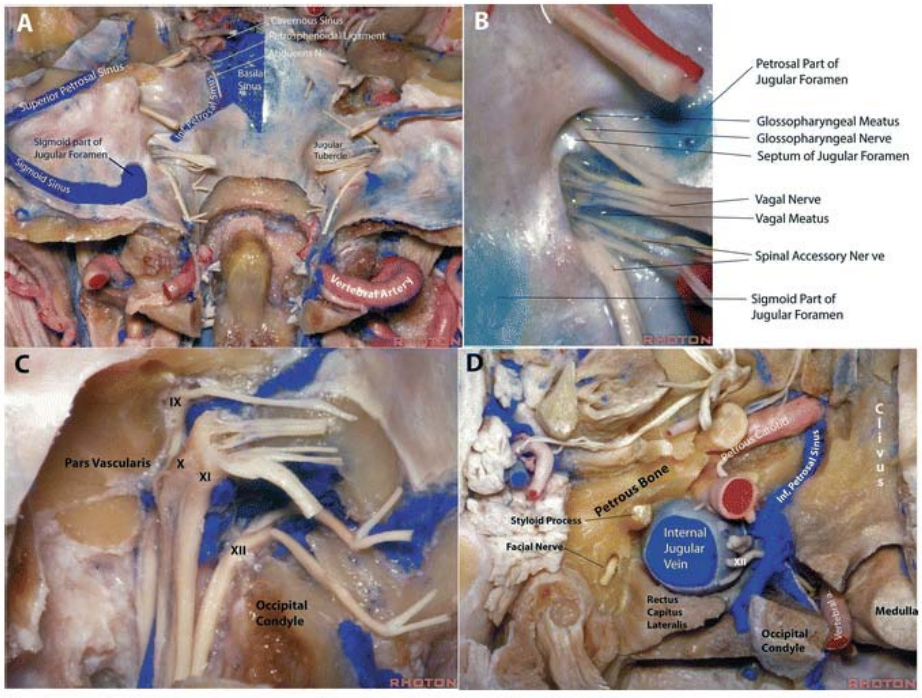
Nel secondo volume è presentata l'anatomia microchirurgica e gli approcci all'area sovratentoriale e alla base cranica anteriore e media. Si compone di nove capitoli che, partendo dalla descrizione degli emisferi cerebrali, spazia verso la vascolarizzazione cerebrale, gli aneurismi cerebrali, l'anatomia e gli approcci chirurgici al sistema ventricolare sovratentoriale, al seno cavernoso e alla sella turcica.
L'intera opera, in lingua inglese, è stata originariamente pubblicata come supplemento alla rivista "Neurosurgery".



L'AUTORE
ALBERT L. RHOTON JR

Albert Loren Rhoton Jr. (18 novembre 1932 - 21 febbraio 2016) nasce a Parvin, nel Kentucky.
Dopo aver frequentato la Washington University Medical School, laureandosi con il massimo dei voti nel 1959, completa il suo internato al Columbia Presbyterian Medical Center di New York City.
Tornato alla Washington University di St. Louis per la sua formazione neurochirurgica, si specializza nel 1964 e nel 1965 inizia una Research Fellowship in Neuroanatomia. Durante tale esperienza matura la consapevolezza dei vantaggi correlati all'uso del microscopio nella ricerca ma anche nella comune pratica neurochirurgica.
Nel 1966 entra nello staff neurochirurgico della Mayo Clinic a Rochester nel Minnesota, dove lavora fino al 1972, quando è nominato Professore di Neurochirurgia e Direttore del Dipartimento di Chirurgia Neurologica dell'Università della Florida. Nel 2014 diventa Direttore del Laboratorio del McKnight Brain Institute.
Durante la sua lunga carriera il Dr. Albert L. Rhoton Jr. è stato Presidente dell' American Association of Neurological Surgeons, del Congress of Neurological Surgeons, della Society of Neurological Surgeons, della North American Skull Base Society, dell'Interdisciplinary Congress on Craniofacial and Skull Base Surgery, della Florida Neurosurgical Society e della International Society for Neurosurgical Technology and Instrument Invention.
Nel 1998 gli è stata conferita la Harvey Cushing Medal, il più alto onore concesso dall'American Association of Neurological Surgeons. E' stato insignito come Honored Guest e Honorary Membership in diverse società neurochirurgiche in Asia, Africa, Europa e Nord e Sud America.
Ha pubblicato più di 250 articoli e vari testi scientifici ed è stato membro del comitato editoriale di sei diverse riviste chirurgiche. Ha ricevuto un "Alumni Achievement Award" dalla Washington University School of Medicine e un "Distinguished Faculty Award" dall'Università della Florida. È stato citato come uno dei migliori dottori in America in diversi libri e anche in pubblicazioni di Good Housekeeping, America's Health e Town and Country.
Fondamentale è stato il suo ruolo nel supportare l'utilizzo del microscopio operatorio nella comune pratica neurochirurgica e nella progettazione di molti degli strumenti microchirurgici oggigiorno di uso comune e che portano il suo nome.
All'Università della Florida ha realizzato la più grande raccolta al mondo di immagini tridimensionali del cervello e ha pubblicato il libro di neurochirurgia più conosciuto e venduto al mondo, pietra miliare per la formazione e costante guida di ogni neurochirurgo, ora in edizione SNO.
Pioniere nel campo della neuroanatomia, Albert L. Rhoton Jr. è riconosciuto a livello mondiale come il "Padre della microneurochirurgia" per i suoi studi neuroanatomici che hanno posto le basi per lo sviluppo delle moderne tecniche neurochirurgiche e hanno rivoluzionato gli approcci chirurgici a molte patologie, compresi i neurinomi dell'acustico e i tumori della base cranica. I suoi studi hanno descritto, con dovizia di particolari, le superfici cerebrali e cerebellari, l'intero sistema ventricolare, i nervi cranici e la complessa rete vasale cerebrale, ponendo attenzione non solo al sistema arterioso, ma anche a quello venoso, in passato spesso trascurato.
La comunità scientifica intera è in debito con il Dr. Albert L. Rhoton Jr. per il suo fondamentale contributo alla descrizione della neuroanatomia e per lo sviluppo e introduzione di una serie di tecniche microchirurgiche il cui fine ultimo è quello di migliorare la sicurezza e l'efficacia della stessa pratica neurochirurgica.

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