

A ten-years history of Isolated Neurosarcoidosis

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Sarcoidosis is a granulomatous, multisystem disease of unknown etiology. Most often the disease affects lungs and mediastinal lymph nodes, but it may occur in other organs. Neurologic involvement of sarcoidosis encompasses a variety of clinical manifestations affecting both central and peripheral nervous system. According to Zagilek's criteria, Neurosarcoidosis (NS) can be diagnosed as definite, probable and possible based on clinical symptomatology, magnetic resonance imaging (MRI) features, laboratory findings, presence or absence of systemic sarcoidosis, exclusion of alternative diagnosis and positive nervous system histology. NS is often suspected in patients with systemic sarcoidosis who develop neurological disorders. However, when sarcoidosis develops exclusively in the nervous system (isolated neurosarcoidosis), its diagnosis is problematic. Isolated NS is considered to be extremely rare, though its exact prevalence has not been determined. At present, there are no set standards for treatment of patients suffering from NS. Early therapy of symptomatic patients is recommended. Corticosteroids still are the first line of treatment for NS patients. In cases of steroids resistance, lack of their effectiveness or existence of contraindication to their use, immunosuppressant treatment is recommended (1,2).

We herewith report the case of a previously healthy 21 years old woman, presenting a subacute visual failure, severe bitemporal headache and amenorrhea. At admission in our Neurological Unit, fundus examination revealed papilledema and visual field examination revealed bitemporal hemianopsia, no other neurological focal sign was found. An endocrinological dysfunction including amenorrhea and diabetes insipidus was found. An MRI of the brain revealed volumetric expansion of the optic chiasm with tenuous hyperintensity on T2-weighted images and inhomogeneous signal increase after gadolinium, a slight increase in volume of the optic nerves in the prechiasmatic tract and a hyperintensity on T2-weighted images of optic tracts bilaterally (**Figure 1**). Blood screening for autoimmune disorders, Quantiferon blood tests, serology for HIV, HBV, HCV, Borrelia, Toxoplasma and Syphilis were all negative. The level of the angiotensin-converting enzyme (ACE) in serum was normal. Cerebrospinal fluid (CSF) analysis revealed 37 cells per cubic millimeter, 44 mg/dL proteins, normal glycorrachia, no oligoclonal bands. Neither Total Body CT scan nor Positron emission tomography revealed extracranial lesions.

Finally a biopsy of the optic nerve was done and histopathology revealed an epithelioid granulomatous lesion without necrosis. Relying on the histological finding, the negativity of the other diagnostic exams and the absence of extracranial lesions, a diagnosis of isolated neurosarcoidosis was made and corticosteroid therapy was early started.

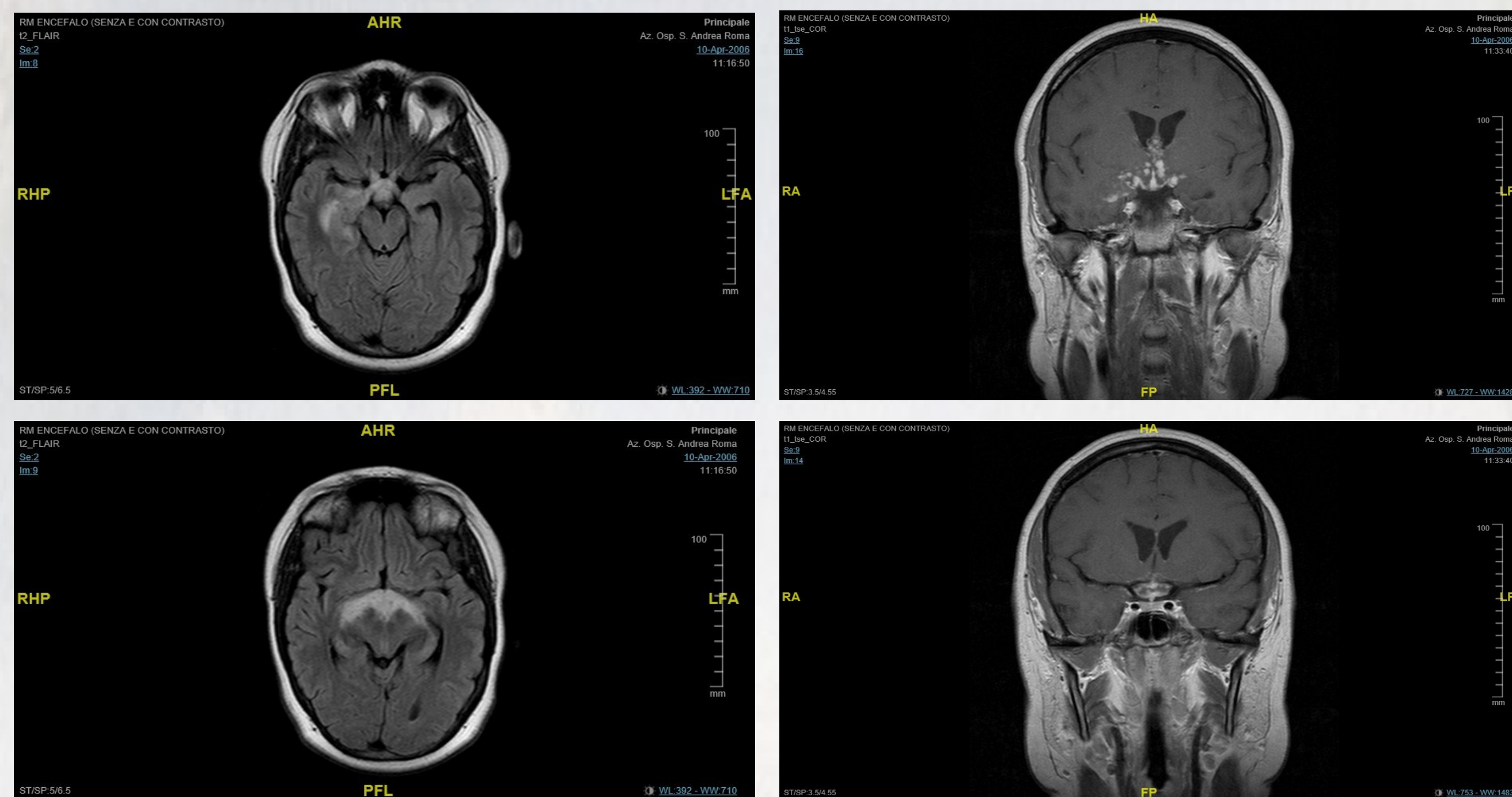


Figure 1 Magnetic resonance imaging on admission: volumetric expansion of the optic chiasm with tenuous hyperintensity, increase in volume of the optic nerves in the prechiasmatic tract and hyperintensity of the optic tracts bilaterally on T2-weighted images; the optic chiasm shown an inhomogeneous signal increase after gadolinium.

The diagnosis of NS is problematic when a patient without a previous history of sarcoidosis presents without any signs of extraneural system involvement. The difficulty of recognition and treatment of this uncommon disorder depends first on non-specific clinical and radiological findings, that can be found almost always in several other (immunological and not) neurological conditions, and then on the lack of comparative trials aimed at assessing the efficacy of the drug treatment in affected patients. Clinical algorithms could be helpful to assess nervous system involvement, but should be integrated with biopsy of affected tissues, because only histopathology can reveal the presence of non-caseating granulomas in the nervous system, the histological hallmark of NS (**Figure 4**) (3). The chronic form of NS is particularly resistant to medical treatments. The use of radiation therapy remains an appropriate option with minimal adverse sequelae if primary medical treatment fails, revealing a partial resolution of clinical features after low-dose whole-brain irradiation of the isolated CNS lesion with 20 Gy (4).

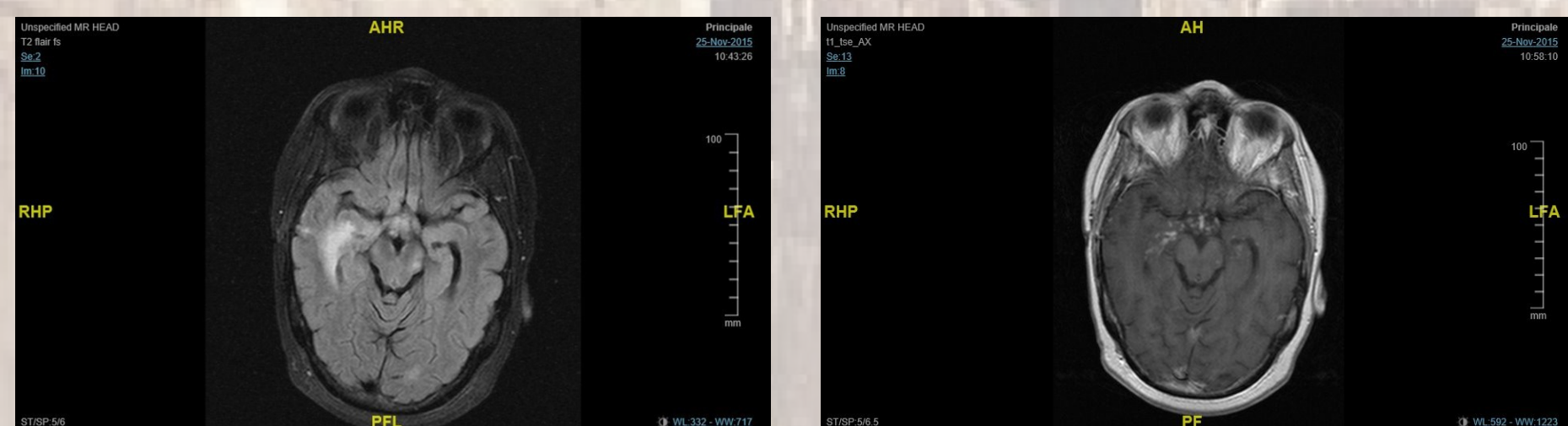


Figure 2 Magnetic resonance imaging showing a relapse of the disease: increasing of the hyperintensity in the right periventricular temporal area in the cortical-subcortical temporo-polar right area and in the fronto basal areas bilaterally on T2-weighted images. There are new areas of hyperintensity on T2-weighted images in the left cerebral peduncle and in the right frontal cortex. The lesions are enhanced after gadolinium.

In the following years, she presented a progressive deterioration of visual impairment up to a complete bilateral amaurosis condition. A second line treatment with an immune-modulating agent was started (Ciclofosfamide 1000/month for 6 months then Methotrexate 15 mg/week for 6 months), with slight benefit. Then she began Infliximab 200 mg/month for 7 months with poor response. Finally she began a low-dose whole brain irradiation (RT WB, 28 Gy) obtaining a partial resolution of the clinical features and a stabilization of disease proved by MRI, for several years. On October 2015, she presented a relapse of the disease detectable by MRI (**Figure 2**) and she underwent to a new cycle of RT WB. Then, because of a clinical worsening, she performed a new MRI, which showed an obstructive hydrocephalus (**Figure 3**) and a ventricle-peritoneum shunt was inserted. Currently her clinical condition is stable and she started Mycophenolato Mofetil in combination with steroid therapy.

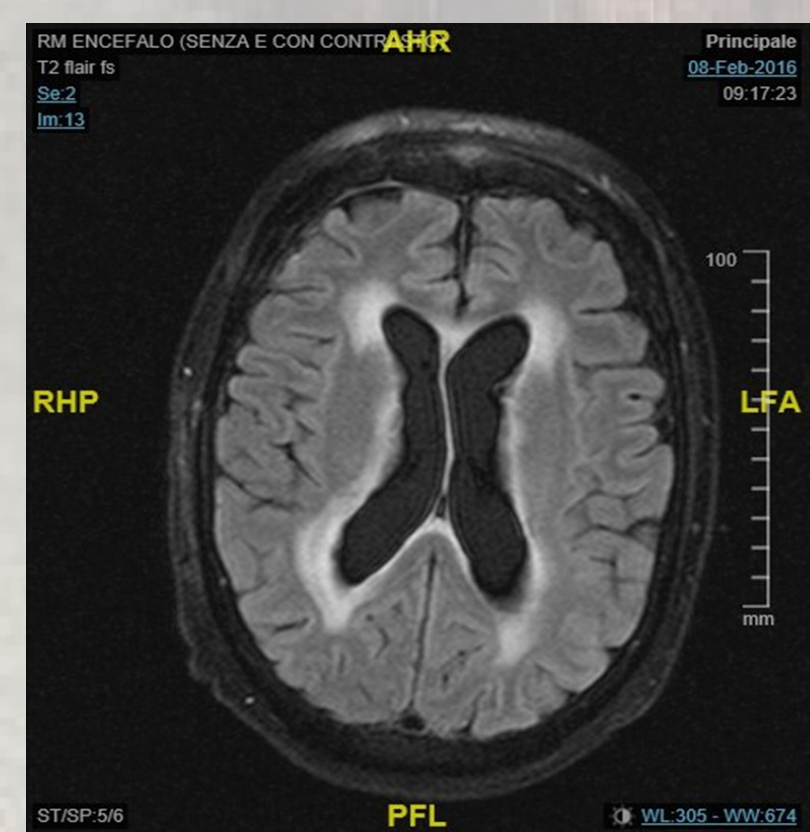


Figure 3 Magnetic resonance showing an obstructive hydrocephalus with transependymal edema.

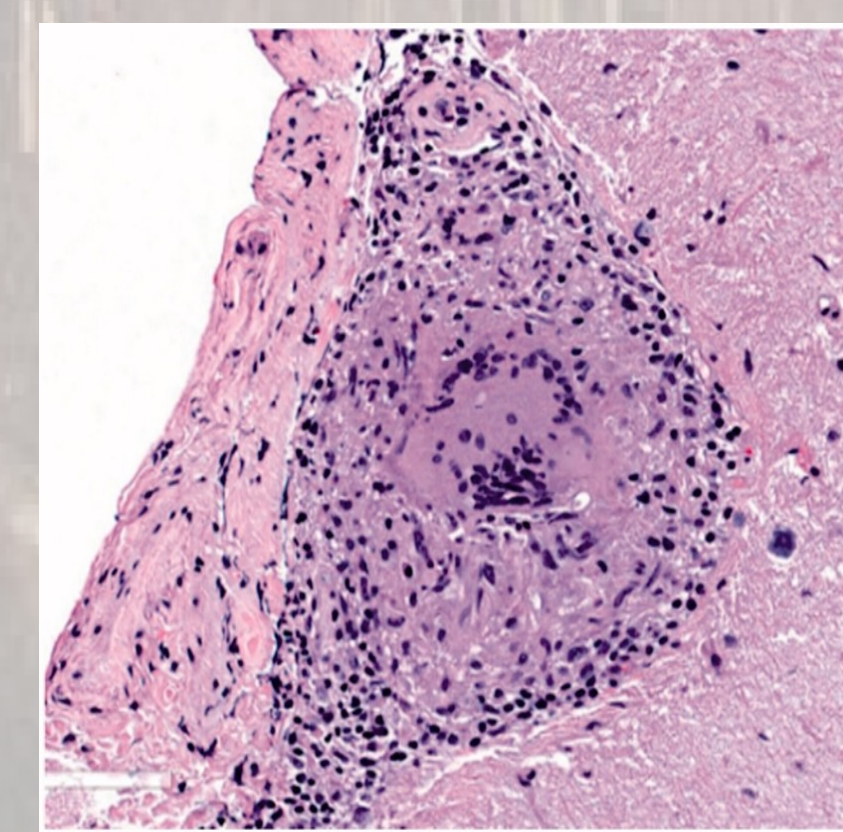


Figure 4 Typical sarcoid granuloma in the subarachnoid space of the cerebellum (H&E stain, original magnification x200): multinucleated giant cells and clusters of epithelioid histiocytes surrounded by lymphocytes expand the subarachnoid space. Underlying cerebellar parenchyma is gliotic (4).

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