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Case Report
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Multiple Sclerosis in a Patient with Vogt-Koyanagi-Harada Syndrome: A Rare Association and a Treatment Challenge

Anguizola Tamayo David Alberto[1], Sanchez Menoyo Jose Luis[1], Artaraz Beobide Joseba Inaki[2], Vidorreta Ballesteros Lucia[1], Vicente Olabarria Inigo[3], Gomez-Beldarrain Marian[1] and Garcia-Monco Juan Carlos[4]*

[1]Department of Neurology, Hospital Galdakao-Usansolo, Spain

[2]Department of Ophthalmology, Hospital Universitario Cruces, Spain

[3]Osatek MRI Unit, Hospital de Galdakao-Usansolo, Spain

[4]Department of Neurology, Hospital Universitario Basurto, Spain

Abstract

The Vogt-Koyanagi-Harada Syndrome (VKHS) is characterized by meningitis, uveitis, and skin lesions. Its association to Multiple Sclerosis (MS) is extremely rare but may condition MS therapy. A 35-year-old female presented with blurred vision, speech difficulties and left-hand clumsiness with multiple brain and spinal cord white matter lesions and oligoclonal banding in the cerebrospinal fluid, consistent with Multiple Sclerosis (MS). She had been previously diagnosed with VKHS on the presence of bilateral granulomatous panuveitis and vitiligo. Her neurological picture was not consistent with the CNS complications that occasionally accompany the VKHS, and thus we concluded that she had a dual pathology. She was initially treated with boluses of methyl prednisolone and, 4 months after admission azathioprine was added considering both conditions with a favourable outcome. This combination is extremely rare and poses a particularly difficult challenge in management, since the immunomodulatory drugs for MS can worsen concomitant autoimmune disorders and therefore may be inappropriate for VKHS. Older drugs like azathioprine may be indicated in this combination of disorders and worked favorably in this patient.

Keywords: Vogt-Koyanagi-Harada syndrome; Multiple sclerosis; Azathioprine; Uveitis

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Correspondence:
Anguizola Tamayo David Alberto, Department of Neurology, Hospital Galdakao-Usansolo, Vizcaya, Spain, E-mail: dvanguizola@gmail.com

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Introduction

Vogt-Koyanagi-Harada Syndrome (VKHS) belongs to the uveo-meningeal syndromes and is characterized by a combination of ophthalmological findings, meningitis, skin lesions, and ear problems [1]. Its association with multiple sclerosis is extremely rare but may lead to diagnostic confusion, since MS may associate uveitis and VKHS may course with neurological disturbances. We describe a patient with VKHS who developed MS, a combination that poses a therapeutic challenge.

Case Presentation

A 32 year-old-woman was admitted for episodes of blurred vision, speech difficulty and left-hand clumsiness. These symptoms appeared simultaneously, lasted 20 sec to 30 sec, and repeated on several occasions daily. Neurological examination was relevant for a visual acuity 0.7 in the right eye and 0.9 in the left eye, attributed to her prior VKHS-related panuveitis. She had irregular pupils with preserved light response, non-painful eye movements, slight dysarthria, bilateral dysmetria in finger-nose maneuver and no Lhermitte sign or meningismus. She was diagnosed with Vogt-Koyanagi-Harada Syndrome (VKHS) 18 years earlier. At that time, she presented with bilateral granulomatous panuveitis that required multiple iridotomies and synechiae release that ultimately resulted in a decreased visual acuity as described on her present examination. Years later, she developed facial vitiligo. The patient rejected systemic immunosuppressive therapy and had been treated with topical corticosteroids. Blood chemistry and an immunological panel (ANA, ANCA, anti-NMO and anti-MOG antibodies) were negative. Low vitamin D levels were detected. Brain MRI (Figure 1) showed multiple brain and spinal cord lesions whose location and morphology resembled MS lesions. Orbital MRI was normal. CSF analysis showed normal glucose, slight increase in proteins, 4-lymphocytes/mm^3, and evidence of intrathecal IgG synthesis, with an IgG index of 1.01 (normal <0.7) and oligoclonal bands in CSF and serum with additional bands

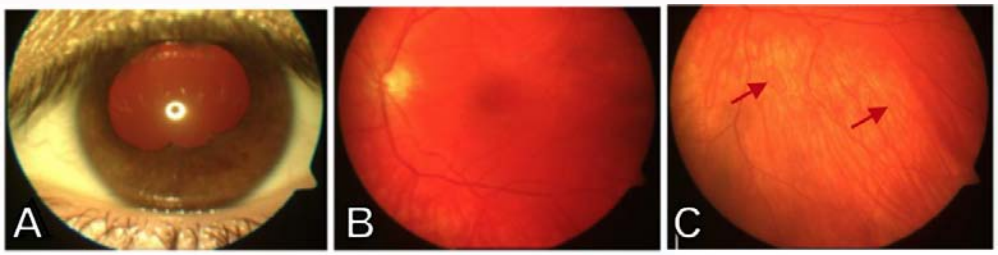

Figure 1: A) Brain MRI (FLAIR sequence) showing multiple lesions affecting supratentorial, infratentorial and cervical regions. Juxtacortical lesion in right frontal operculum, B) Diffuse subcortical lesions and periventricular lesions with Dawson finger-like morphology, C) Right temporal and right mesencephalic lesion (arrow) and cervical lesion at the height of C_2. There were no abnormalities in the optic nerves, and there were no gadolinium-enhancing lesions (not shown).

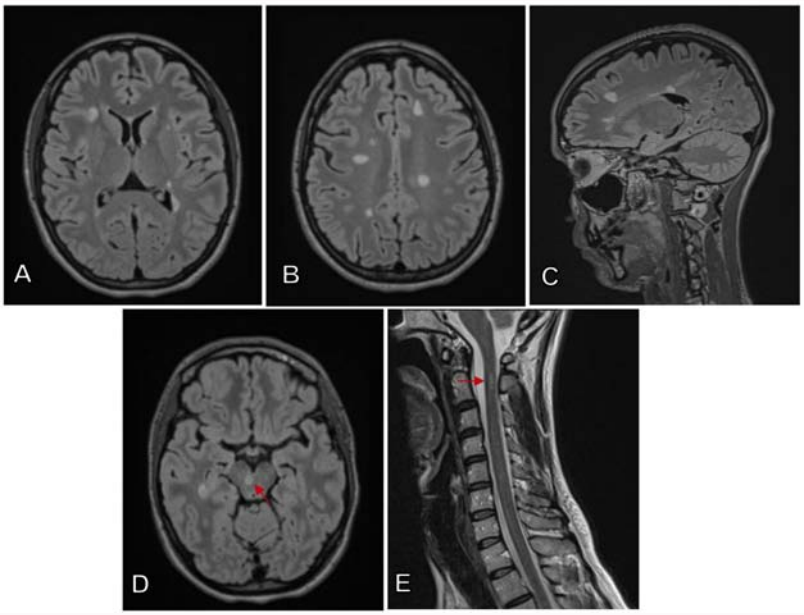

Figure 2: Ocular findings in this patient. A) Anterior synechia, B) Sunset glow fundus, C and D) Dalen-Fuchs nodules (arrow). These findings represent chronic lesions of panuveitis, affecting the anterior uvea (synechia), E) intermediate uvea (Dalen Fuchs nodules) and posterior uvea (around the optic nerve) and are characteristic of VKHS.

in CSF. Visual evoked potentials showed a W morphology and an abolished electroretinogram in the right eye. HLA-B57 was negative. The ophthalmological examination is summarized in Figure 2. These investigations suggested a demyelinating disorder of the CNS, meeting the 2017 McDonald criteria for space and time dissemination in Multiple Sclerosis (MS) [2].

In view of the findings, her clinical symptoms were interpreted as paroxysmal episodes of MS and were attributed to the brainstem lesions as evidenced in her brain MRI. The patient was given a diagnosis of MS in association to VKHS. A course of methylprednisolone 1 g daily for 3 days was administered with complete symptomatic relief, followed by a tapering regimen of oral steroids. She was discharged on low dose oral prednisone, vitamin D supplements, and to topical corticosteroids.

After considering all therapeutic options, we prescribed azathioprine 125 mg bid plus prednisone 2.5 mg qd4 months after admission because of its activity against both diseases. One month later, the ophthalmologist planned a new surgery. After the placement of an intravitreal dexamethasone implant followed by cataract surgery and release of synechiae, a visual acuity of -1 was obtained in the right eye and of 1 in the left eye. Cranial MRI 3 months later revealed a new lesion, clinically silent, in the knee of the corpus callosum. The patient has remained stable, without further relapses, for one and a half years. However, the control cranial MRI 2 years after the diagnosis of MS shows 4 new supratentorial lesions (left frontal, corpus callosum knee and splenium and right retrolenticular); cervical spinal MRI with persistent C_2 lesion. No new outbreaks, but paroxysmal episodes of cramp and paresthesias in the left hand and leg several times a day along with mild dysarthria are present. Instead, uveitis has remained stable. Therefore, we decided to suspend azathioprine and started dimethyl fumarate due to its good safety profile and the need for fewer analytical controls, considering the pandemic due to COVID-19.

Discussion

Our patient presented with paroxysmal neurological deficits and evidence of several CNS white matter lesions, meeting the McDonald criteria for MS. She also met the criteria for incomplete VKHS (involvement of eyes and skin, sparing meningeal and auditory/vestibular symptoms) [1]. Importantly, a diagnosis of MS requires the exclusion of other plausible explanation for the neurological disturbances. The question arose as to whether VKHS was responsible for all her findings. VKHS consists of a combination of recurrent meningitis and bilateral uveitis with retinal changes.

The typical ocular findings and vitiligo were present in this patient, although meningitis was absent. Brain lesions in VKHS have been occasionally reported but differ from those of MS. There is a single report describing lesions in deep brain structures and mesencephalon, whose morphology does not resemble MS; furthermore, pleocytosis was present and oligoclonal bands were absent in the CSF [3]. Diffuse white matter involvement with nodular lesions has also been reported in another patient [4]. More often, brain MRI in VKHS is normal. One percent of MS patients will develop uveitis, usually an intermediate variant, sparing the anterior and posterior uvea, in contrast to the global panuveitis of VKHS [5]. The association of VKHS and MS is extremely rare and has been described to our knowledge only once. In that case, the diagnosis of MS was first, and the patient received treatment with corticosteroids and IFN-beta, a obtaining a satisfactory outcome [6]. The combination of these conditions represents a challenge in patient management. IFN-beta, a first-line drug in MS, may trigger or exacerbate autoimmune conditions like NMO spectrum disorders, lupus nephritis, Raynaud's syndrome, thyroid disease, myasthenia gravis, hemolytic uremic syndrome, autoimmune hepatitis and neuropathy [7,8]. Given the autoimmune background of VKHS, we chose azathioprine for this patient based on its action in both entities and the possibility of adding other immunomodulator agents in the future. Azathioprine and methotrexate have been proven safe in combination with other immunomodulator in MS [9,10]. Considering the novel treatments for MS, there is no experience regarding their use in VKHS.

Conclusion

MS may be associated to VKHS, posing an important treatment challenge. Despite the newer therapeutic options in MS, older drugs may offer a better profile.

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