

CASE REPORT

Pattern recognition is a sequential process—accurate diagnosis and treatment 20 years after presentation

Dimos Merinopoulos^{1,*}, Janak Saada², Colin Jones³ and Chetan Mukhtyar¹¹Rheumatology Department, Norfolk and Norwich University Hospital, Norfolk, UK, ²Radiology Department, Norfolk and Norwich University Hospital, Norfolk, UK, ³Ophthalmology Department, Norfolk and Norwich University Hospital, Norfolk, UK

*Correspondence address. Rheumatology Department, Norfolk and Norwich University Hospital, Norfolk, UK, 01603 287211.
E-mail: dmerinopoulos@yahoo.com

Abstract

A 25-year-old woman presented with ophthalmic and neurological manifestations. Her ocular manifestations included bilateral uveitis, multifocal retinal phlebitis, vitreitis and multiple retinal haemorrhages. Her neurological manifestations included migrainous headaches with visual aura, transient sensory symptoms and posterior circulation Transient Ischemic Attack (TIA). Magnetic resonance imaging of the brain demonstrated lesions that involved the deep white matter lesions initially and progressed to also involve the juxta cortical white and deep grey matter and brain stem, but without further neurological manifestations. She was sequentially treated with intravenous and oral glucocorticoid, cyclophosphamide and mycophenolate mofetil, but she continued to suffer with persistent episodes of retinal haemorrhages. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Susac syndrome and Behcet's disease were considered in the differential diagnosis. Genetic workup and clinical picture were not suggestive of the former two. Further history of oro-genital ulceration in younger age emerged, which pointed strongly towards a diagnosis of Behcet's disease with neurological involvement. She was treated with infliximab and methotrexate with complete resolution of her symptoms and withdrawal of corticosteroids for the first time in over two decades.

CASE REPORT

A 25-year-old woman presented in 1994 to the ophthalmology department with sustained episodes of flashes affecting the vision in both eyes. She was morbidly obese weighing 140 kg and a smoker. On examination, her optic discs and fundi were normal, but she was noted to have a transient drop in her visual acuity that normalized over a few days. For the on-going troublesome migrainous phenomenon, she was referred to neurology where she reported episodes of blurred vision, paraesthesia in the left lower jaw, left arm and leg. She was experiencing monthly right-sided headaches, associated with photophobia, which resolved within 24 hours. Examination was normal with no evidence of focal neurological deficit. Multiple sclerosis was

considered as a diagnosis but later deemed unlikely. She was thought to have complicated migraine, and she was discharged. In 1998, she was re-referred to the neurology department with intermittent tingling on both sides of her body. This was accompanied by a sensation of imbalance. She had some short lasting visual obscuration. Neurological examination was normal. A magnetic resonance imaging (MRI) of the brain was organized but could not be performed due to morbid obesity. In 2002, she presented to the emergency eye department with bilateral granulomatous uveitis. Retinal funduscopy revealed multifocal retinal periphlebitis. The optic discs appeared healthy, and there was no retinal cystoid macular oedema. Blood tests showed a normal ANA, antiphospholipid screen, full blood count, an ESR of 28 mm/hour and the presence

Received: January 9, 2019. Revised: April 4, 2019. Accepted: May 11, 2019

© The Author(s) 2019. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

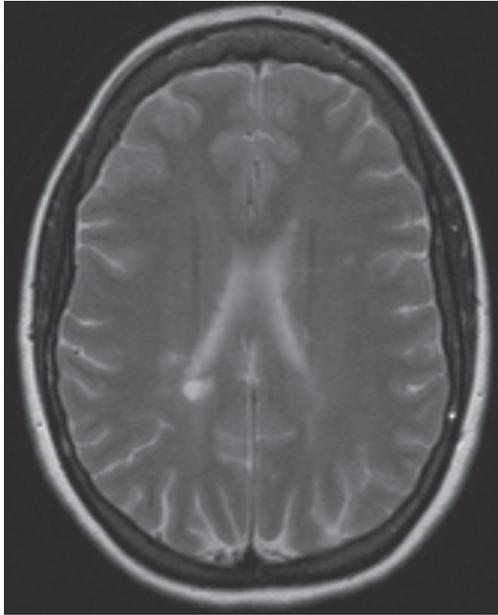


Figure 1: MRI of the brain in 2002 demonstrating lesions that involved the deep white matter.

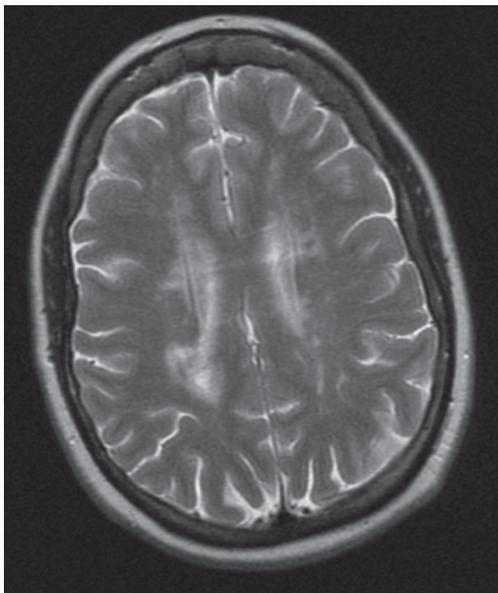


Figure 2: MRI of the brain in 2005 demonstrating progression of the number and distribution of white matter lesions with multifocal deep grey matter and brain stem involvement (on lower sections not shown).

of an atypical ANCA. The ANCA prompted a referral to the rheumatology department. An MRI of the brain showed lesions that involved the deep white matter (Fig. 1). Over the next few years, she was monitored in a combined rheumatology–neurology clinic. Neurological examination remained normal. A Lumbar Puncture (LP) was not performed due to the body habitus. Visual evoked potentials were normal. Between 2002 and 2004, she had episodes of vitritis, hypopyon and macular oedema needing large doses of oral prednisolone. There was debate about this being a demyelinating process versus a vasculitis process, and it was decided that she should be treated with six cycles of intravenous cyclophosphamide followed by

mycophenolate mofetil. However, in spite of the treatment, in 2005 she had a further episode of retinal haemorrhage and a posterior circulation transient ischaemic attack. A repeat MRI of the brain revealed progression of the number and distribution of white matter lesions with multifocal deep grey matter and brain stem involvement (Fig. 2). Considering this to represent small vessel disease, possibly due to vasculitis, she was commenced on aspirin, b-blocker and statin. From 2004–2010, she continued to have attacks of uveitis and retinal bleeds, which were treated with a high dose of prednisolone. At this stage, an MRI was repeated to monitor the central nervous system changes. The MRI demonstrated progressive disease, which is, though non-specific, more suggestive of multifocal small vessel disease. The unusual distribution of the lesions and clinical progression sparked the search for alternative diagnoses. A review of the entire history and a multi-disciplinary discussion between the ophthalmology, rheumatology and neurology departments considered potential differential diagnoses—CADASIL, Susac syndrome and neurological Behçet's disease. A negative genetic screen ruled out CADASIL. The lack of auditory involvement made Susac syndrome unlikely. Further history of intermittent oral and vaginal ulcers in her teens was obtained. This history had been lost because the patient had not considered this to be important and this had not been a problem for a number of years because of on-going oral prednisolone (doses of > 10 mg daily). A clinical diagnosis of Behçet's disease was made. She fulfilled the classification criteria as set by the International Study Group for Behçet's disease [1]. She was commenced on infliximab and azathioprine in 2013, which was later switched to methotrexate due to azathioprine intolerance. Since then she had no further episodes of uveitis, and her subsequent MRIs of the brain revealed stable appearances. At last follow-up she remained stable and is back in full-time employment.

DISCUSSION

Behçet's disease is a systemic vasculitis of unknown aetiology involving vessels of all sizes, characterized by orogenital ulceration, ocular and neurological involvement. Its clinical manifestations may not occur simultaneously; therefore, a high index of suspicion is required, and a detailed past history is crucial to its diagnosis [2]. A diagnosis of cerebral and retinal vasculitis had been made and sustained in medical notes in our patient. The finding of temporal lobe atrophy in such a young woman caused us to look for more sustainable diagnoses—leading to a definite diagnosis of Behçet's disease. She presented initially with vague migrainous headaches with visual aura, transient sensory symptoms and episodes of blurred vision. Initial ophthalmological and neurological examinations were normal. Years later she re-presented with bilateral uveitis, which persisted for years, and also developed a posterior circulation stroke. She was treated for retinal vasculitis with systemic immunosuppression (cyclophosphamide and mycophenolate mofetil) with recurrence of uveitis episodes [3]. Interestingly her neurological examination and cognition remained normal throughout the years. Her MRI of the brain demonstrated progressive white matter, deep grey matter and brain stem disease consistent with multifocal small vessel disease. Her non-response to treatment triggered a re-consideration of her case after many years of having been classified as cerebral and retinal vasculitis. Further history elicited a past episode of oral and genital ulcers in her teen age years, which she did not complain of because they had always been steroid responsive, and she did not consider them to be

relevant. On the basis of the MRI lesions, re-current episodes of uveitis and orogenital ulcers, she was diagnosed with Behçet's disease and commenced on Infliximab and azathioprine as per the EULAR recommendations [4–6]. Correct identification of the nature of the vasculitis illness and treating it with the correct medication resulted in excellent long-term outcomes resulting in no further retinal bleeds and a return to full-time employment.

KEY LEARNING POINTS

It is important to re-evaluate patients with long-term diagnoses when the clinical profile does not fit. It is easy to be biased with previously made diagnoses. But logical re-interpretation of existing data can provide plausible alternatives.

Classification of vasculitis is not just for academic purposes. Correct classification leads to correct medical treatment, which in-turn leads to better patient-related outcomes.

Behçet's disease is a clinical diagnosis that can present with sequential manifestations. Vasculitis should be thought of as a diagnosis in all patients with multi-organ involvement.

ACKNOWLEDGEMENTS

This paper is made open access by the generosity of the Norfolk and Norwich Hospital Charitable Funds.

CONSENT

Received

FUNDING

No funding received.

REFERENCES

1. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;**335**: 1078–80.
2. Yazici H, Fresko I, Yurdakul S. Behçet's syndrome: disease manifestations, management, and advances in treatment. *Nat Clin Pract Rheumatol* 2007;**3**:148–55.
3. Cuchacovich M, Verdaguer JI, Gatica H, López JM, Verdaguer J. Treatment of ocular inflammatory disease with glucocorticoids and cyclophosphamide pulses [article in Spanish]. *Rev Med Chil* 1995;**123**:865–73.
4. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease: an open-label trial. *Arthritis Rheum* 2005;**52**:2478–84.
5. Sfikakis PP, Markomichelakis N, Alpsoy E, Assaad-Khalil S, Bodaghi B, Gul A, et al. Anti-TNF therapy in the management of Behçet's disease—review and basis for recommendations. *Rheumatology (Oxford)* 2007;**46**:736–41. Epub 2007 Apr 2.
6. Sfikakis PP, Theodossiadis PG, Katsiari CG, et al. Effect of infliximab on sight threatening panuveitis in Behçet's disease. *Lancet* 2001;**358**:295–6.