

6-1964

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Raul Calderon

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### Recommended Citation

Calderon, Raul (1964) "Behcet's Disease With Neurological Involvement," *Henry Ford Hospital Medical Bulletin* : Vol. 12 : No. 2 , 205-209.

Available at: <https://scholarlycommons.henryford.com/hfhmedjournal/vol12/iss2/6>

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## BEHCET'S DISEASE WITH NEUROLOGICAL INVOLVEMENT

RAUL CALDERON, M.D.\*

THE TRIAD OF recurrent oral and genital ulcerations and ocular lesions is known as Behcet's disease, after Behcet a professor of dermatology at the University of Istanbul who first demonstrated in 1937<sup>1</sup> that these three symptoms occur as a distinct entity and not as manifestations of such well known diseases as syphilis, tuberculosis or rheumatism. One or another combination of these symptoms were described as early as 1722.<sup>2-6</sup> The oral and genital ulcerations are usually sharply circumscribed, superficial and tender, with a grayish yellow center and may be surrounded by an erythematous halo. The ocular lesions include uveitis, iridocyclitis with hypopyon, papillitis, optic atrophy, retinitis, choroidoretinitis, detachment of the retina, thrombosis of either retinal arteries or veins, keratitis and conjunctivitis.<sup>7</sup> Less common manifestations include involvement of the joints, erythema nodosum, ulceration of skin and gastrointestinal tract, thrombophlebitis and central nervous system disease.<sup>8-9</sup>

The most important and essential character of this disease is its recurrence. It may begin with any one of the triad of symptoms, usually oral or genital ulcerations, and the complete syndrome may not appear until several years later. The condition is essentially chronic, and some cases have been "followed up" for as long as 20 years. Blindness is a frequent sequel. When neurologic complications are present, however, the mortality rate rises, and death occurs frequently within one year from onset of neurologic signs. This disease is not limited to any one geographical location as it was believed before.<sup>8</sup> The etiology is unknown.

A patient with Behcet's disease and neurological involvement managed with steroid therapy is presented in the following report.

### CASE REPORT

A 38-year-old right-handed white female was admitted to this hospital on March 5, 1964. Her past history revealed an appendectomy and tubal ligation in 1952. No family history of diabetes or neurological diseases was elicited.

From 1957 to 1961 the patient complained of recurrent genital ulcers which reappeared again in March 1963 and have been present intermittently since. She has also had recurrent ulcers of her oral mucosa and palate during the last two years.

In June 1963 she had an abrupt onset of severe pain at the top of her head associated with general malaise. Two or three days later, she began to notice gradual onset of clumsiness

\*Division of Neurology.

of the right hand and weakness of the right lower extremity, associated with blurred vision in the left eye which progressed to almost complete blindness. Subsequently her vision improved somewhat but the clumsiness of the right-sided extremities persisted through July and the latter part of August when she again had an episode of severe headache accompanied by loss of vision in the left eye and some blurring on the right.

She was hospitalized elsewhere and said to have had a fever of 103°; she was treated with antibiotics and her temperature was said to return to normal. Examination at that time showed right hemiparesis and blurring of the margins of both discs especially on the left. Retinal hemorrhages were also present on the left. Bilateral carotid arteriograms were performed and reported as normal. A lumbar puncture revealed C.S.F. protein 35 mg, glucose 55 mg, R.B.C's 34, W.B.C's 70, colloidal gold curve 1221100000. EEG was normal. Her condition became progressively worse and cortisone therapy was instituted because of the possibility that her symptoms might represent acute multiple sclerosis. A definite improvement was noted in regard to her hemiparesis and visual deficit. She was discharged on tapering doses of cortisone. On Dec. 24, during the third week off of cortisone, she experienced pain over the left eye which became noticeably red with increasing blurring of vision.

On January 16, 1964 she was admitted to another hospital. The examination at that time revealed a mild right-sided hemiparesis with hyperactive reflexes and a Babinski. Examination of the left eye showed blurring of disc margin with white exudates in the retina, vitreous detachment and extensive diminution of central visual fields on the left.

Laboratory studies revealed normal electrolytes, B.U.N., serum creatinine, fasting blood sugar, glucose tolerance test, P.B.I., hemogram, uric acid and urinalysis. Blood serology, agglutination test for *Brucella abortus*, skin tests for fungi and L.E. cell prep were negative. A protein electrophoretic pattern showed minimal elevation of alpha two and beta globulins. A lumbar puncture showed an opening pressure of 225 mm of water, C.S.F. was clear with 2 W.B.C's, protein 41 mg, serology negative, sugar 76 mg, chloride 124 mEq., colloidal gold curve of 011000000; C.S.F. was also negative for fungi and acid fast bacillus. An E.K.G. showed sinus tachycardia. A pap smear was negative. A muscle biopsy showed minimal fatty atrophy. Brain scan and E.E.G. were normal. Skull, chest and optic foramina X-rays were normal. Gynecology diagnosed a monilial vaginitis. Oral surgery found abscesses of the left second maxillary bicuspid and right upper molar which were treated with penicillin and extraction after incision and drainage.

She continued getting progressively worse and again was placed on steroids (Prednisone 40 mg daily) with rapid objective improvement of eye and extremity findings. Again she was discharged on tapering doses of prednisone and local eye steroids. Less than two weeks after discharge while still on 25 mg. of Prednisone daily, she again developed headache with left eye pain, general malaise, worsening of the blurred vision in the left eye and of the weakness in the right extremities. At this time she was admitted to this hospital.

General physical examination on admission revealed an oriented, somewhat sleepy and slightly obese white female. Her temperature was 98°F, B.P. 135/90 mm. Hg, pulse 80 per minute, and resp. 24 per minute. There were multiple small aphthous ulcers on the oral and genital mucosa. Neurologic examination disclosed a moderate right hemiparesis including the face with hyperactive reflexes and a Babinski. Ophthalmologic evaluation revealed neuroretinitis, optic papillitis, posterior vitreous detachment, mild iridocyclitis and evidence of occlusion of the lower temporal branch of the retinal artery on the left eye.

Laboratory studies revealed normal electrolytes, B.U.N., creatinine, hemogram, urinalysis, prothrombin time, sed rate, protein electrophoresis and blood smear. Blood serology was negative. 2 hs. pc. blood sugar was 155 mg., L.E. cell prep was neg. Lumbar puncture showed a pressure of 180 mm. of water. The C.S.F. was clear, examination revealed protein 53 mg, W.B.C's 14 (lymphocytes), serologic tests negative, colloidal gold curve 1111000000. An E.K.G. showed non-specific T wave changes. The E.E.G. showed hypersynchrony of the alpha rhythm of uncertain clinical significance. Chest and skull X-rays were negative.

On admission prednisone was increased to 40 mg. daily and within forty-eight hours there was objective improvement in the left eye and right-sided neurologic signs. Fourteen days later the patient showed hardly any paresis though the reflexes remained hyperactive and the Babinski present. The left eye had cleared remarkably though with persistent diminution of central fields. She was discharged on 37.5 mg of prednisone to be followed in the O.P.D.

#### DISCUSSION

A review of the literature revealed 38 reported cases of Behcet's disease with involvement of the nervous system.<sup>10-23</sup> The estimated frequency of neurological com-

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plications varies from 10 to 25 per cent.<sup>8-14</sup> It affects mostly males in a proportion of 3 to 1.<sup>7</sup> The age of onset of the neurological complications varied from 16 to 61 years of age with an average of 37 years. The initial signs of Behcet's disease occurred from two weeks to more than 27 years before the appearance of neurological involvement.<sup>23</sup> The neurological symptoms manifest the basic and essential character of the disease since they are also recurrent in nature. With the exception of the lower motor neuron any part of the neuraxis may be involved at any one time and with recurrence the involvement may migrate from one part to another.

Seizures (focal or generalized), aphasia, hemiparesis, quadriplegia, organic mental syndromes, pseudobulbar palsy and extra pyramidal signs may develop indicating cortical and subcortical structure involvement. Multiple cranial nerves palsies, may occur with involvement of the brain stem. Cerebellar signs and spinal cord involvement manifested by spastic paraplegia or Brown-Sequard syndrome have also been reported. Meningeal irritation is frequently present.

The cerebrospinal fluid cell count may be normal, though in the majority of cases, pleocytosis (usually less than 60 cells per cu.mm) was present, and the highest count recorded has been 5,400 cells per cu.mm. These may be either polymorphonuclear or lymphocytes. In over 50 per cent of cases the level of protein was greater than 50 mg. per cent; the highest value reported has been 5200 mg. per cent. The C.S.F. pressure usually is normal though it may be increased. Electroencephalograms have been non-specific.

The mortality rate in the 38 cases with neurological complications was 47 per cent; two thirds of these deaths occurred within one year from the onset of neurologic signs.<sup>23</sup>

*Differential Diagnosis.* — In the absence of oral and genital ulcerations the evaluation of neurological signs may present some difficulty. The course of recurrences and remissions and the evidence of multiple lesions with involvement of brain stem and pyramidal tract may strongly mimic multiple sclerosis or arteriosclerotic occlusive vascular disease in the elderly patient. Syphilis of the central nervous system is excluded by serologic testing of the blood and C.S.F. Sarcoidosis<sup>24</sup> may be excluded by lack of prominent lymphadenopathy and pulmonary lesions and negative Kveim test associated with the known predilection of sarcoid for the facial nerve, hypothalamus and pituitary region. Vogt-Koyanagi-Harada's disease<sup>25</sup> may also be confused with Behcet's disease. This is likewise a disease of unknown etiology, characterized by meningeal irritation, bilateral diffuse exudative choroiditis or uveitis, with neuroretinitis and papillitis followed by retinal detachment. Various degrees of alopecia and depigmentation of hair and skin and auditory disturbances accompany these findings.

*Pathology.* Post-mortem examination has been performed in 10 cases. The most frequent abnormalities in the central nervous system<sup>20 22-26</sup> have been peri-vascular and meningeal infiltration with lymphocytes, plasma cells and macrophages, in addition

to small foci of softening in the grey and white matter, often in relationship to blood vessels. In all cases demyelination and gliosis were minimal and intranuclear or cytoplasmic inclusions were absent.

The evidence to support the viral, allergic or vascular origin of this disease, is considered to be inconclusive.<sup>23-27</sup> The pathological character of the lesions offers no definite lead to the etiology although it favors the viral theory.

#### THERAPY

The treatment of the ocular signs and neurologic complications with steroids has produced variable results. Some authors believe that steroid therapy is dangerous because of the likelihood that the disease is caused by an infectious organism.<sup>28</sup> Several cases<sup>18-21</sup> have not shown favorable response to dosages of cortisone ranging from 50 to 200 mg. daily. On the other hand Wadia and Williams<sup>10</sup> reported improvement in one patient with meningoencephalitis who was treated with 100 mg. of cortisone per day. Whitty's patient<sup>12</sup> developed severe neurological deficit while on 50 mg. of cortisone per day with subsequent improvement after 18 days on 60 mg of prednisone daily. Schotland's case<sup>23</sup> was treated on two separate occasions with prednisone in dosages of 100 mg. per day for periods of two weeks each. The second day off of steroids after the first two weeks of therapy the patient had an exacerbation of neurological symptoms. Our patient was treated on three separate occasions with steroids, the last two with prednisone in dosages of 40 mg. daily. On all three occasions there was a definite improvement of ocular and neurological symptoms. During the second course of steroids the symptoms recurred while tapering the prednisone to 25 mg daily, with subsequent improvement when the prednisone was increased to 40 mg. In our case, steroid therapy did not increase the severity of the patient's ocular and neurological involvement. On the contrary it benefited the patient's condition, though the effect on the over-all course of the disease is uncertain. Steroids although beneficial may convert this disease into a chronic disorder eliminating the spontaneous remissions. This is similar to the situation which may be developing in some cases of giant cell arteritis<sup>29</sup> treated with steroids. We believe that the high morbidity and mortality known to exist when ocular and neurological involvement are present may be reduced with the use of steroid therapy in large dosages for prolonged periods of time.

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