LESSON OF THE MONTH

Jarisch-Herxheimer reaction in a patient with neurosyphilis

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Abstract

A 40 year old man presented with progressive personality changes in the previous six months. Specific serological tests for syphilis in blood and CSF were highly positive and CSF sedimentation showed signs of an inflammatory process. Ten hours after the start of penicillin treatment a severe symptomatic Jarisch-Herxheimer reaction with alteration of level of consciousness, pupillary changes, and focal neurological signs developed.

Jarisch-Herxheimer reaction may occur in various settings, particularly in the treatment of syphilis. Investigation of CSF before the treatment may predict a potential risk. Corticosteroid treatment has been suggested for prevention.

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An increase in Jarisch-Herxheimer reaction may be expected, related to an increase in the incidence of neurosyphilis due to a rise in primary and secondary syphilis in connection with HIV infections.[1 2] In late syphilis treated with penicillin, neurosyphilis constitutes the chief hazard. Jarisch-Herxheimer reaction has been reported to occur in up to 75% of patients with dementia paralytica (general paralysis of the insane).[3] The clinical spectrum of Jarisch-Herxheimer reaction varies. Minor reaction includes febrile temperatures, headache, myalgia, and malaise. Some patients with Jarisch-Herxheimer reaction have convulsions, an altered state of consciousness, focal neurological signs, and psychiatric manifestations. Fatalities due to Jarisch-Herxheimer reaction in patients with late syphilis have also been described.[3 4]

Case history

A 40 year old white man, an unskilled worker, was admitted with progressive personality changes. There was a history of primary syphilitic infection 17 years previously. Specific serological tests for syphilis in blood and CSF were highly positive (table). Cytology of CSF showed 24/mm^2 cells and sedimentation showed signs of an inflammatory process with activated lymphocytes, granulocytes, and phagocytes. Protein concentration in CSF was 1·56 g/l (normal range 0·15–0·45 g/l).

The patient was orientated with reduced concentration, memory loss, tendency to perseveration, and impairment of reasoning and critical faculties. Productive psychosis did not occur. Physical examination, routine serum chemistry, EEG, and CT (with and without contrast enhancement) were normal. Cranial MRI showed T1 weighted hypointense and T2 weighted hyperintense (not sharply delinated) lesions towards the underlying white matter in both frontal lobes. The adjacent cortex was thinned, and CSF spaces over both frontal lobes were slightly enlarged.

After starting intravenous treatment with 5 million units of sodium penicillin G every four hours, a symptomatic Jarisch-Herxheimer reaction developed. Ten hours after the first dose of penicillin the patient was febrile (38·8°C), sweating, and had a heart rate of 120–140 beats/min. The level of consciousness was fluctuating. He developed anisocoria with sluggish pupillary light reaction, but unimpaired pupillary near reaction.

The next day his temperature returned to normal, but he remained disorientated with psychomotor restlessness. In the subsequent days, as well as impaired consciousness, lateralisation of tendon reflex accentuation changed several times. Although he could understand plain commands, he was only able to utter simple words. The focal neurological signs disappeared within one week. An atonic bladder with urinary retention and overflow developed and persisted for several months.

An EEG on the first day of Jarisch-Herxheimer reaction showed generalised abnormality with 3/s rhythmic activity (periodic lateralised epileptiform discharges), which has been described in patients with neurosyphilis.[5–7] The rhythmic activity disappeared within a week, but generalised changes persisted; EEG returned to normal

Serological results

	March 1991		*September 1991*		*March 1992*	
	Blood	*CSF*	*Blood*	*CSF*	*Blood*	*CSF*
VDRL	1:1	1:1	–	–	–	–
TPHA	1:40960	1:20840	1:10240	1:5120	1:10240	1:1280
FTA-ABS	+	+	+	+	+	+
IgM-SPHA	1:8	1:4	1:8	1:4	1:8	1:2

+ = Reactive; – = non-reactive; VDRL = venereal disease research laboratory slide test; TPHA = *Treponema pallidum* haemagglutination assay; FTA-ABS = fluorescent treponemal antibody-absorption; IgM-SPHA = IgM-Solid-phase haemabsorption.

after two weeks. Repeated CT was normal. A meningovascular syphilis therefore seemed unlikely.

The response to treatment was confirmed by specific tests for syphilis six months and one year later (table).

Discussion

Historically the discovery of syphilis was quickly followed by the recognition of an acute reaction precipitated by specific treatment.[8] The overt clinical features of the reaction were described in 1895 by Jarisch[9] and in 1902 by Herxheimer and Krause.[10]

Similar reactions have been reported after treatment of other spirochetal infections (louse-borne relapsing fever, Vincent's angina, rat bite fever, leptospirosis, yaws),[11] other bacterial infections (brucellosis, tularaemia, glanders, and anthrax),[11] and of African trypanosomiasis.[12] Singular reports describe Jarisch-Herxheimer reaction in treatment of *Pneumocystis carinii* pneumonia,[13] meningococcal meningitis,[14] and falciparium malaria.[15]

In neurosyphilis Jarisch-Herxheimer reaction may take one or both of two forms: either a transient rise in temperature, chill, headache, malaise, myalgia during the first 24 hours after treatment with the drug (asymptomatic type) or an exacerbation of mental symptoms or other neurological signs during the first days (symptomatic type).

In the symptomatic type the variety of manifestations is related to the type of neurosyphilis. Patients with asymptomatic neurosyphilis rarely have Jarisch-Herxheimer reaction. Patients with dementia paralytica may react with convulsions, exacerbations of the existing psychoses, or focal neurological signs. The symptoms of patients with tabes dorsalis (locomotor ataxia) consisting of lightning pains, urinary retention, and constipation may be temporarily intensified during treatment or may appear for the first time. Jarisch-Herxheimer reaction may also be lethal, particularly in patients with gummas of the brain or coexisting mesaortitic aneurysm.[3]

No recent data are available concerning the incidence of Jarisch-Herxheimer reaction in neurosyphilis. In older reports[16,17] asymptomatic reactions occur in 13% to 54%, symptomatic reactions in 1·7% to 11% of patients.

Pathogenesis of Jarisch-Herxheimer reaction remains poorly understood. Numerous mechanisms, such as release of treponemal breakdown products,[9] hypersensitisation phenomena,[18] allergic origin,[19] endotoxaemia,[20] and opioid withdrawal reaction[21] have been proposed, but the exact cause remains obscure.

Histologically, Jarisch-Herxheimer reaction is manifest by acute inflammatory changes within syphilitic lesions. Capillaries and veins become congested, followed by swelling of the endothelial cells. Polymorphonuclear neutrophils and mononuclear leucocytes migrate through the vessel wall into the surrounding oedematous connective tissue.[22] A peripheral leucocytosis and lymphopenia usually accompanies these histological alterations.[4]

Jarisch-Herxheimer reaction cannot be predicted on reliable indices. The frequency of reactions increases proportionally with white cell count and total protein in CSF. Hoekenga *et al*[17] found the highest incidence of Jarisch-Herxheimer reaction in patients with dementia paralytica and in whom both cell count and protein content in CSF were raised. Incidence is not related to race or sex, duration of infection with syphilis, serological titre, or dose of penicillin. Luetic manifestations such as gummas of the brain and of the larynx,[3] aortic aneurysm due to syphilitic aortitis,[3] luetic optic neuritis,[23] and involvement of the auditory nerve[24] have been described as having a potential risk for a dramatic course of Jarisch-Herxheimer reaction.

The value of steroids in prevention of Jarisch-Herxheimer reaction remains unproved. Corticosteroids have been reported to exert some positive effect,[25,26] and the use of corticosteroids (30–50 mg prednisone) before antibiotic treatment is recommended.[27,28] Although corticosteroids are able to reduce fever, they are not thought to prevent symptomatic Jarisch-Herxheimer reaction.[29] It has been argued that the benefits they provide may be outweighed by the risks involved.[26] In luetic organ manifestations like gumma and mesaortitis luetica, the use of corticosteroids seems justified.

Other attempts to prevent Jarisch-Herxheimer reaction by treatment with antihistamines, bismuth, and initial use of low doses of penicillin have been unsuccessful.[4,30,31] Meptazinol has been shown to diminish the Jarisch-Herxheimer reaction of louse-born fever,[21,32] but its use with treatment of syphilis has not been reported.

Treatment of Jarisch-Herxheimer reaction depends on symptoms. The occurrence of Jarisch-Herxheimer reaction is not an indication for discontinuing treatment. It is useful to monitor cardiovascular function and control temperature every two hours during the first 48 hours from the start of any treatment for neurosyphilis.

Although Jarisch-Herxheimer reaction in neurosyphilis is rare and usually the asymptomatic type occurs, a symptomatic form may take a dramatic course, as in our patient, with deterioration of existing symptoms and the occurrence of additional neurological symptoms.

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