SHORT REPORT

Sodium fusidate in Gillain-Barré syndrome: a case report

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Abstract

A patient with Guillain-Barré syndrome is reported on who responded favourably to a short course treatment with the novel immunosuppressant sodium fusidate (Fucidin), given at a daily dose of 1.5 g for one week. Along with prompt and clear cut clinical improvement, treatment with Fucidin was associated with a rapid decline in the blood concentrations of inflammatory cytokines presumably implicated in the pathogenesis of Guillain-Barré syndrome such as interleukin-2, interferon-γ, and tumor necrosis factor-α. The ex vivo production of these cytokines was also markedly diminished compared with pretreatment values. Fucidin was well tolerated and no clinical or biochemical side effects were seen.

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Guillain-Barré syndrome is a heterogeneous syndrome which may be due to a demyelinating or axonal neuropathy probably autoimmune in nature, that is clinically characterised by acute progressive and symmetric motor weakness of the limbs and of bulbar and facial musculature[1 2] We report on a patient with severe Guillain-Barré syndrome who responded favourably to a short course of treatment with the novel immunosuppressant sodium fusidate (Fucidin; see Nicoletti *et al*[3] for a review.

Case report

A 46 year old woman developed progressive weakness in the legs and after few days in the arms. Two weeks after the onset of symptoms the patient was admitted to hospital. Neurological examination showed severe weakness of the lower limbs and less marked weakness in the upper limbs, with the absence of deep tendon reflexes. She was unable to walk 5 m with a walking frame. No cranial nerve involvement was noticed.

Examination by EMG disclosed reduced motor conduction velocity in all limbs, particularly in the lower limbs (median nerve 44 m/s; ulnar nerve 53 m/s; right exterior sciatic popliteal (ESP) 32 m/s, left ESP 33 m/s, posterior tibial nerve 32 m/s). The sensory conduction was normal. Needle EMG showed fibrillation and positive sharp waves in all muscles examined. Brain and spinal MRI were normal: Chest radiography and abdominal echography were performed to exclude neoplasms and showed no abnormalities. Analysis of CSF showed an abnormal total protein concentration (111 mg/dl), a high concentration of albumin (65.2 mg/dl), IgG 11.3 mg/dl, and a cell count of 0.8/mm^3.

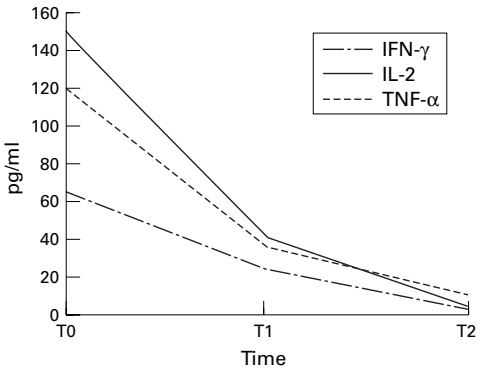
At immunological analysis, the patient showed raised blood concentrations of interferon (IFN)-γ, interleukin (IL)-2, and tumour necrosis factor (TNF-α). These cytokines are usually not detectable in the blood of normal healthy subjects.[4 5]

The diagnosis of Guillain-Barré syndrome was made according to the Asbury diagnostic criteria.[6]

The degree of motor function was expressed on a seven point functional scale as used in previous trials: 0=healthy; 1=minor signs or symptoms but fully capable of manual work; 2=able to walk>10 m without assistance; 3=able to walk>10 m with a walker or support; 4=bedridden or chairbound (unable to walk 10 m with a walker or support); 5, requiring assisted ventilation for at least part of the day; and 6, dead. At entrance our patient was assigned a 4 disability grade.

After obtaining informed consent from the patient, she was treated orally with sodium fusidate (Fucidin, Sigma-Tau, Pomezia, Rome, Italy). at a dose of 1.5 g (two tablets before each of the main meals) for one week. No other treatment or rehabilitation was previously performed.

Three days after the start of treatment the patient was able to stand up from her bed and to maintain a standing position without assistance. After 10 days she was able to walk (grade 2) and presented a progressive improvement in the motor deficits of the arms. The patient was discharged at grade 1 and rehabilitative treatment was started. These clinical effects were accompanied by a progressive and marked reduction in the circulating concentrations of IFN-γ, IL-2, and TNF-α; the values were reduced>50% in each patient after three days of treatment and further declined below the



Reduction of IFN-γ, IL-2, and TNF-α blood concentrations in a Fucidin treated patient with Guillain-Barré syndrome. Blood samples were obtained before (T0), and 3 (T1) and 7 (T3) days after treatment with 1.5 g/day Fucidin. Blood samples were allowed to clot at room temperature and serum was immediately separated by centrifugation at 1000 g and stored at -20 °C until cytokine measurements by enzyme linked immunosorbent assay (ELISA). The kits for detection of IFN-γ and IL-2 were provided by Genzyme (S Francisco, CA, USA) and that for TNF-α by Cistron Biotechnology (Pine Brook, NJ, USA). The lower limit of sensitivity of the assays were 3 pg/ml for IFN-γ, 4 pg/ml for IL-2, and 10 pg/ml for TNF-α. Samples with undetectable cytokine concentrations were assigned the lower limit of sensitivity of the assays as a theoretical value.

threshold of detection of the assays at the end of treatment with Fucidin (figure). The ex vivo production of these cytokines from peripheral blood mononuclear cells was also strongly diminished compared with pretreatment values; phytohaemagglutinin induced IFN-γ and IL-2 production declined from 321 to 109 pg/ml and 201 to 56 pg/ml respectively, and lypopolysaccharide induced TNF-α release diminished from 476 to 137 pg/ml. Treatment with Fucidin was well tolerated and no clinical, biochemical, or haematological side effects were noticed.

At clinical follow up, performed after 6 months, the patient showed no modification of the clinical grade. All deep tendon reflexes were normal except for the bilateral achilles reflexes. A neurophysiological study showed an improvement of the motor conduction velocity (median nerve 52 m/s; right ESP 44 m/s and left ESP 44 m/s). Neurological examination at the 1 year follow up showed a slightly distal muscular strength deficit of the left arm, but all the deep tendon reflexes were normal. She reported frequent night cramps. Motor conduction velocities were normal. The patient was able to perform normal daily activities.

Discussion

Proinflammatory cytokines such as IL-2, IFN-γ ,and TNF-α may play an important part in the pathogenesis of Guillain-Barré syndrome.[2] Because Fucidin suppresses IL-2, IFN-γ ,and TNF-α production in vitro and in vivo[7–12] we tested its effects in one patient with Guillain-Barré syndrome. The prompt beneficial clinical response was associated with a rapid decline of IL-2, IFN-γ ,and TNF-α blood concentrations as well as with their diminished ex vivo secretion. This suggests, but does not prove, that an inhibitory effect of Fucidin on the production of these cytokines might have favoured recovery.

Although most patients spontaneously recover from Guillain-Barré syndrome, the course of the disease might be severe, leading to severe tetraparesis which requires artificial ventilation in about 20% of the patients, with a long lasting and costly stay in intensive care units, and with residual deficits occurring in 5%-10% of the patients.[1 2] The course of the disease is favourably modulated by plasmapheresis[13] and high dose intravenous gammaglobulin.[14] However, these approaches are expensive and, in the case of plasma exchange, technically difficult, and alternative therapies are much needed.

Because Fucidin was only tested in a single case of Guillain-Barré syndrome, and in view of the autoremitting course of the disease, no firm conclusion can be drawn on the utility of this drug in the treatment of Guillain-Barré syndrome. None the less, evidence for a possible therapeutic effect is strenghtened by previously noted beneficial effects of Fucidin in the treatment of other immunoinflammatory diseases in rodents and humans.[8 10 11 15–19] Moreover, that recovery of our Fucidin treated patient occurred much earlier than usual (2–4 weeks after cessation of progression[2]), also suggests a causal relation to treatment with Fucidin. Along with the rare and reversible side effects of Fucidin,[3] this case report warrants larger studies on use of this drug in Guillain-Barré syndrome.

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NEUROLOGICAL STAMP

Carlos Juan Finlay y Barres (1833-1915)

Finlay was born in a little town in Puerto Principe in Cuba. His father was a Scottish physician and his mother of French origin. They had come to Cuba via Trinidad and his father established a successful practice in medicine, especially in ophthalmology. Finlay started his medical studies at the Jefferson Medical College in Philadelphia where he graduated in 1855. After spending one year with the neurologist Silas Weir Mitchell, he went to Paris and studied neurology and ophthalmology. In 1857 he began practising in Havana. He was a general practitioner but specialised in ophthalmology and soon became attracted to infectious disease and epidemiological problems in Cuba. Finlay's ophthalmological publications dealt with a case of exophthalmos due to tumour, a new method of cataract extraction, the complications of atropine, visual disturbances caused by malaria and by quinine, and binocular vision.

When in 1881, Dr Carlos Finlay advanced the theory that yellow fever was transmitted by the bite of a species of the mosquito Aëdes, he was ridiculed by his medical colleagues. His ideas were ignored for 20 years. Finlay was struck by the presence of the mosquito *Aëdes aegypti* in houses during epidemics and noted that the yellow fever and mosquito season seemed to coincide. But, following the suggestion of Finlay, one of the greatest triumphs of modern hygiene occurred with the conquest of yellow fever by the United States Army Yellow Fever Board (1900), consisting of Walter Reed (1851-1902), James Carroll (1854-1907), Jesse W Lazear (1866-1900), and Aristide Agramonte (1869-1931). As no animals could be made to develop the disease, Carroll volunteered to be bitten by an infected mosquito and developed yellow fever but, fortunately, recovered. Lazear, bitten by an infected mosquito, died after a few days of illness. The army, under the leadership of Dr William C Gorgas (1854-1920) established the vector and calculated the incubation period. By destroying the mosquitoes Havana was freed of yellow fever for the first time in 150 years. The construction of the Panama canal was made possible by using the same methods. Before Gorgas freed the isthmus of yellow fever and other dangerous infections, the area was almost uninhabited by the white race, and was known as the "white mans' grave". In 1927 three Nigerian physicians, Adrian Stokes, Johannes H Bauer, and N Paul Hudson confirmed that the yellow fever agent was a filterable virus and in 1937 Max Theiler, a South African microbiologist working at the Rockerfeller Foundation, developed an effective vaccine.

Finlay was honoured philatelically by Cuba in 1934 in the 100th year of his birth (Stanley Gibbons 399, Scott 319). Finlay was also honoured by postmarks.

Finlay's son Carlos Edouard Finlay (1868-1944), who became Professor of Ophthalmology of Havana University in 1907 and later Director of Charities of Havana, President of the First National Cuban Medical Congress, and Dean of the Medical Faculty and Director of Public Health in Cuba, has also been honoured philatelically in a stamp issued by Cuba in 1965.

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