Treatment of brain fever – breakthrough in sight

Scientists at the National Brain Research Centre, Manesar, have reported a significant step forward in the search for a suitable treatment of the dreaded Japanese encephalitis (JE) disease. Commonly known as 'brain fever', JE is a viral disease leading to inflammation of the brain, and kills roughly one-third of its victims. Children are more susceptible to the disease than adults and an estimated 80% of those affected by the virus are children. Of the two-thirds that survive the disease, around half are left with severe disabilities, including cognitive impairment as also motor and behavioural disorders. The JE virus lives in wild birds and pigs and is transmitted by mosquitoes, but does not spread from person to person.

There are no specific antiviral agents for the treatment of JE and treatment available so far is only supportive. Basu and Mishra[1] have experimented with the use of the antibiotic minocycline on JE-infected laboratory animals and have reported encouraging results. Brain tissue taken from minocycline-treated JE-infected mice was studied in comparison with that of mice which had been similarly infected, but not dosed with the antibiotic. Results showed significant decrease in inflammation of the brain tissue. It was also seen that treatment with minocycline could significantly decrease loss of healthy neuronal cells. A decrease in viral load and reduction in expression of proteins associated with stress were also noted in the brain tissue studied.

In humans, JE has an incubation period lasting between 5 and 15 days. Given the fact that mice were treated with minocycline the day after they were inoculated with the JE virus, would minocycline administered at a much later date show similar positive results? Also, do we know if treatment with minocycline could reduce the disabilities of those who survive the disease? 'We will know the answers to those questions only after clinical trials have been carried out on humans', says Basu. 'We have seen a significant decrease in inflammation of the brain tissue and that is very encouraging', he mentions. Basu reports that the Department of Biotechnology has shown interest in initiating clinical trials on the use on minocycline on JE-infected patients.

Minocycline has in fact shown good results in the treatment of several neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, etc. in other experimental studies. In addition, minocycline is a relatively inexpensive and easily available drug. Commenting on the results, M. M. Panicker (National Centre for Biological Sciences, Bangalore) says, 'This is a very nice finding – especially important to India. The finding is certainly sufficiently interesting to warrant human trials. I hope the researchers involved also investigate the possible use of the drug as a prophylactic'.

Basu and Mishra conclude in their paper that '. . . Minocycline at relatively low doses is a very effective neuroprotective drug against an experimental model of JE even when the administration is started next day following viral inoculation, indicating a clinically relevant therapeutic time window for this tetracycline derivative'.

More recently, Basu and Das[2] have reported that the disease affects not just brain cells, but also neural stem cells. Basu explains that the disease infects the subventricular zone (SVZ) of the brain (Figure 1) – the region of the brain responsible for neurogenesis. The virus does not lead to the death of the neural stem cells in the SVZ, but inhibits their ability to proliferate.

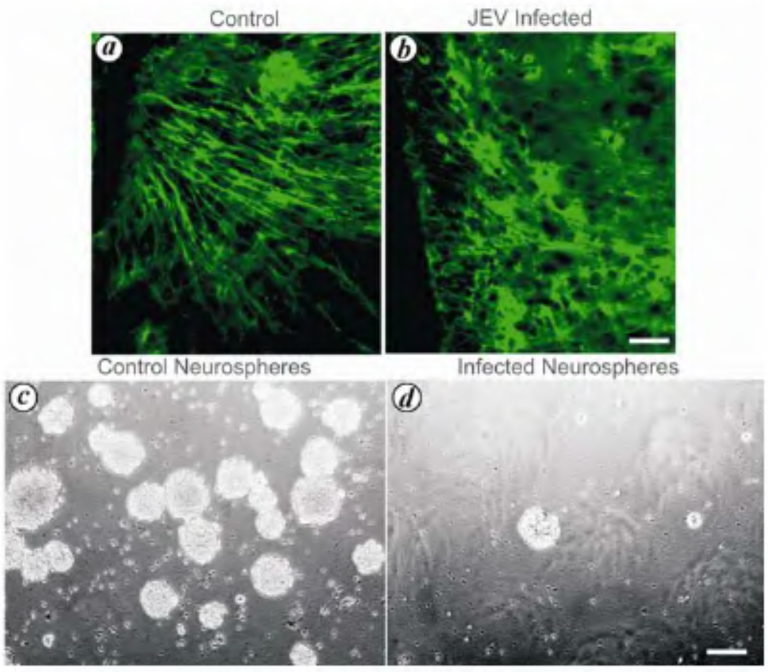

Figure 1. Japanese encephalitis virus (JEV) infection causes loss of proliferating neural progenitor cells from the subventricular zone (SVZ), and the resultant impairment in neurosphere formation. BALB/c mouse pups were either JEV-infected or PBS (phosphate buffered saline solution)-injected (control) and sacrificed after 4 days, when symptoms appeared. ***a***, Immunohistochemistry performed on cryostat sections for nestin (a marker for neural progenitor cells), shows a decrement in nestin-positive cells in SVZ of JEV-infected mice. ***b***, Single-cell suspensions from SVZ of control and JEV-infected mouse pups were cultured in the presence of growth factors and allowed to form neurospheres (free-floating aggregates of minimum eight cells). Neurospheres isolated from JEV-infected animals were distinctively lesser in number and smaller in average size than those from control animals. Scale bar corresponds to 100 μm. (Courtesy: Das S. and Basu, A., National Brain Research Centre, Manesar).

1. Mishra, M. K. and Basu, A., *J. Neurochem.*, 2008, **105**, 1582–1595.
2. Das, S. and Basu, A., *J. Neurochem.*, 2008, **106**,1624–1636.
3. http://en.wikipedia.org/wiki/Japanese_encephalitis

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