# Japanese encephalitis virus causes 'double trouble' to brain

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Japanese encephalitis (JE), commonly known as brain fever, is one of the prevalent mosquito-borne encephalitis in India and entire South East (SE) Asia. Besides resulting in thousand fatalities each year, JE virus (JEV) infection causes prominent neurological sequelae in approximately one-third of the survivors. Even those patients in the good recovery group commonly encounter psychiatric problems, which include mental retardation, learning disabilities, speech and movement disorders and behavioural abnormalities.

Recent research in National Brain Research Center, Manesar, India by Dr. Anirban Basu and his graduate student, Sulagna Das have shown that JE virus damages the brain in two ways, by not only killing brain cells but by preventing the birth of new cells from neural stem/progenitor cells (NPC) and depleting the NPC pool in the brain. "It's a double hit to the brain, the JE virus causes brain injury by killing neurons as well as prevents its repair" lead researcher and the senior author of the work Anirban Basu said in a statement.

The children are more vulnerable targets of this virus, which causes massive neuronal loss in the Central Nervous System. "Children are at a dynamic stage of brain development, hence infection at this stage can have devastating effects on mental functions later in life. Our study has tried to explore how JEV infection leads to development of long-term cognitive deficits in the survivors", says Dr. Anirban Basu who has been working in the neurobiology of JEV infection for the past 4 years. These findings have been published online in a paper in *Journal of*

*Neurochemistry* for inclusion in a future issue of the journal.

"The breakthrough here is that the JE virus prevents neural stem and progenitor cells in the brain from dividing; it hangs them up," Basu said. "It's the first time that a mosquito-borne virus has ever been shown to affect neural stem cells." The progressive infection in these cells eventually results in decrease in proliferation ability, providing a possible explanation for their diminished pool upon infection," said Basu. He also went on to state, "The neurological and cognitive deficits in the JE survivors could be related to the drop in NPC cells in the neurogenic region of the brain called the subventricular zone".

Neural stem/progenitor cells are the saviours of the brain following any insult or infection and via the process of neurogenesis help the recovery process. These cells have the ability to self-renew over lifetime and generate both neurons and glia, which make up the CNS. The initial work with neural stem cells in cell culture dishes interestingly showed that unlike neurons, these stem cells are a resilient population and do not undergo robust cell death upon JEV infection. Instead, the virus lowers the NPC pool by disrupting the growth kinetics and the proliferative ability of these cells. The study was extended in mouse models of JE, where a significant decrease in the actively proliferating NPCs was observed in the subventricular zone or the primary niche of post-natal neurogenesis.

The possible mechanism by which JEV reduces the proliferating NPC pool was also worked out by the scientists utilising the cell cycle studies. Sustained proliferation is a key feature of NPCs, which have to pass through various cell cycle checkpoints and phases of division. Upon JEV infection, these cells halt at the resting phase and fail to proceed to the dividing S-phase. Both cell culture and animal studies indicate that JEV inhibits the DNA synthesis in these cells during progressive infection and induces cycle arrest in them. The researchers went on to show that

the virus leads to increased expression of certain checkpoint proteins that block the transition of cells to S-phase, thus preventing the NPCs from multiplying.

Over the years, JE has become a major cause of mortality and morbidity in wide areas of SE Asia. The very high incidence of permanent and disabling neurological sequelae has considerable socioeconomic impact. "Knowing the mechanism, we can start to approach this therapeutically" Basu said. "This indicates that we might eventually treat this form of neurological and psychiatric problems by either ramping up brain repair or protecting the repair mechanism," Das added.

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