The pubertal divide in mortality from severe influenza: clues for novel therapeutics

The 1918 influenza pandemic, also known as the Spanish flu, was a protracted and devastating outbreak. Upwards of 500 million people worldwide were infected and death estimates surpassed 50 million. Contemporary studies using virus reconstructed from autopsy samples confirm that this particular virus was extraordinarily virulent.

However, the horrible record of the 1918 pandemic includes a fascinating observation that may lead to novel therapeutics to help treat severe influenza in our own time. We refer to the striking differences in mortality between age groups. Young adults between the ages of 18-30 fared the worst, but one group did extraordinarily well. Children between the ages of 5-14 were infected at the highest rate among all groups but had the lowest mortality. With the onset of puberty (around age 14 during the 1918 pandemic), the mortality rates started to climb. The resilience of children, and the change in disease death rates with puberty, has been observed with other infectious diseases such as tuberculosis and malaria but is poorly characterized. In other to explore the mechanisms that may underlie childhood resistance to flu, we used a mouse model.

The experimental model consisted of mice at different stages of puberty. Young mice that had not gone into puberty (prepubertal mice) and older mice that had gone into puberty (pubertal mice) were infected with the H1N1 influenza virus and monitored for 21 days for morbidity and mortality. We found much less mortality in the prepubertal mice of both sexes (16%) when compared to the high death rate in the pubertal mice (71%).

We also used pharmacological and surgical manipulations to directly test the effect of pubertal onset on influenza mortality. Young mice received a drug that delays the onset of puberty (GnRH antagonist) and were infected with flu. Mice with delayed puberty had much better survival when compared to mice with normal puberty. To further test the effect of puberty, we compared influenza mortality in mice whose gonads were surgically removed (thereby physically preventing the onset of puberty). The gonadectomized mice had much better survival compared to normal mice. Interestingly when mice with surgically removed gonads were given estrogen replacement they lost their resistance to flu infection and had the same rate of mortality as mice with intact gonads. The deleterious effect of estrogen informed our decision to explore more studies to directly test the role of estrogen as a mediator of flu mortality.

Gene expression studies identified sex hormone and related molecules consistent with a deleterious role for the increased estrogen production that occurs during puberty in both sexes. Treatment of both male and female mice three days after flu infection with a drug that block estrogen’s effect resulted in markedly improved survival. We also found that interleukin-1 beta (IL-1b), a pro-inflammatory molecule, was increased in mice that had gone through puberty. When we treated pubertal mice that a drug that neutralized the IL-1 molecule these mice survived flu at

higher rates then untreated mice.

Our findings suggest that the surge of estrogen that occurs with puberty contributes to an excessive and harmful immune response that results in poor outcomes. We think tour findings help explain the remarkable childhood resistance to mortality from severe infections exemplified in the 1918 influenza pandemic. More importantly, our experimental work in mice has identified a number of promising targets for drug development. Blocking molecules associated with the high mortality seen after puberty may allow adults with severe infections to have the better outcomes seen in children.

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