

Newborn foals may offer clues to autism

February 4 2015, by Pat Bailey



UC Davis School of Veterinary Medicine professor and researcher John Madigan, inspects a maladjusted foal at Victory Rose Thoroughbreds in Vacaville, Calif. on Jan. 21, 2015. Credit: Joe Proudman / UC Davis

Veterinary researchers at the University of California, Davis, are teaming up with their colleagues in human medicine to investigate a troubling disorder in newborn horses and are exploring possible connections to childhood autism. The common link, the researchers suggest, may be abnormal levels of naturally occurring neurosteroids.

The horse disorder, known as neonatal maladjustment syndrome, has puzzled horse owners and veterinarians for a century. Foals affected by the disorder seem detached, fail to recognize their mothers and have no interest in nursing.

"The behavioral abnormalities in these foals seem to resemble some of the symptoms in children with autism," said John Madigan, a UC Davis veterinary professor and expert in equine neonatal health.

The maladjustment syndrome in foals also caught the attention of Isaac Pessah, a professor of molecular biosciences at the UC Davis School of Veterinary Medicine and a faculty member of the UC Davis MIND Institute, who investigates environmental factors that may play a role in the development of autism in children.

"There are thousands of potential causes for autism, but the one thing that all autistic children have in common is that they are detached," Pessah said

Madigan, Pessah and other researchers in veterinary and human medicine recently formed a joint research group and secured funding to investigate links between the two conditions.

Maladjusted foal syndrome

In newborn foals, [neonatal maladjustment syndrome](#), or dummy foal syndrome, occurs in 3 to 5 percent of live births. With around-the-clock bottle or tube feeding plus intensive care in a veterinary clinic for up to a week or 10 days, 80 percent of the foals recover. But for horse owners, that level of care is grueling and costly.

For years, the syndrome has been attributed to hypoxia—insufficient oxygen during the birthing process. Madigan and UC Davis veterinary

neurologist Monica Aleman began sleuthing around for other potential causes, however, noting that hypoxia usually causes serious, permanent damage, while most foals with the maladjustment syndrome survive with no lingering health problems.

One of their prime suspects was a group of naturally occurring neurosteroids, which are key to sustaining pregnancies in horses, especially in keeping the foal "quiet" before birth.

Foals remain quiet in the womb

"Foals don't gallop in utero," Madigan is fond of saying, pointing out the dangers to the mare if a four-legged, hoofed fetus were to suddenly become active in the womb. The prenatal calm is made possible, he explains, by neurosteroids that act as sedatives for the unborn foal.

However, immediately after birth, the infant horse must make an equally important transition to consciousness. In nature, a baby horse would be easy prey for many natural enemies, so the foal must be ready to run just a few hours after it is born.

In short, somewhere between the time a foal enters the birth canal and the moment it emerges from the womb, a biochemical "on switch" must be flicked that enables the foal to recognize the mare, nurse and become mobile. Madigan and Aleman suspect that the physical pressure of the birthing process may be that important signal.

"We believe that the pressure of the birth canal during the second stage of labor, which is supposed to last 20 to 40 minutes, is an important signal that tells the foal to quit producing the sedative neurosteroids and 'wake up,' " Madigan said.

Neurosteroids persist in the bloodstream

The theory, he says, is supported by the fact that the maladjusted foal syndrome appears more frequently in horses that were delivered via cesarean section or experienced unusually rapid births. Perhaps those foals do not experience significant physical pressure to trigger the change in neurosteroids, Madigan said.

Furthermore, the research team has found for the first time that sedative neurosteroids persist, and their levels often rise, in the bloodstream of foals born with symptoms of the maladjustment syndrome. These neurosteroids are known to be able to cross the blood-brain barrier and impact the central nervous system, acting on the same receptor as do sedatives and anesthetics.

The researchers also have demonstrated that maladjustment symptoms can be brought on temporarily in normal, healthy foals by administering short infusions of a neurosteroid called allopregnanolone. When the neurosteroid levels drop, the foals return to their normal state.

Foals 'wake up' with gentle harness pressure

Amazingly, the veterinary researchers have found that they can reduce maladjustment symptoms in foals by using several loops of a soft rope to gently squeeze the foal's upper torso and mimic the pressure normally experienced in the birth canal. When pressure is applied with the rope, the foal lies down and appears to be asleep.

After 20 minutes—about the same time a foal would spend in the [birth canal](#)—the rope is loosened and the squeeze pressure released. In initial cases, the foals have responded well to the procedure and recovered, some rising to their feet within minutes and then bounding over to join

the mare and nurse.

The researchers suspect that the pressure triggers biochemical changes in the central nervous system that are critical for transitioning the foal from a sleeplike state in the womb to wakefulness at birth.

While larger studies are underway, the researchers have presented their results at national and international meetings of equine veterinarians, and many veterinarians and clinics are treating maladjusted foals with the squeeze procedure—now called the [Madigan Foal Squeeze Procedure](#).



UC Davis School of Veterinary Medicine professor and researcher John Madigan squeezes a maladjusted foal at Victory Rose Thoroughbreds in Vacaville, Calif. on Jan. 21, 2015. The squeezing simulates the foal's trip through the birth canal. Madigan's research has found the squeezing to help the foal recover from Neonatal Maladjustment Syndrome, sometimes within hours. Credit: Joe Proudman / UC Davis

Madigan cautions that, in spite of the strong observational effects, a larger, controlled clinical trial of national and international scope is now needed to reproduce those observed results and provide a better understanding of the mechanisms at work in the foals.

Foal behaviors resemble autism

The early findings have compelling implications for the health of newborn foals, and have caused the researchers to also explore possible links to autism, which includes a group of complex brain-development disorders. While the symptoms vary, these disorders are generally marked by difficulties with social interactions, verbal and nonverbal communication, and repetitive behaviors.

"The concept that a disruption in the transition of fetal consciousness may be related to children with autism is intriguing," said Pessah, noting that the behaviors seen in the maladjusted foal syndrome truly are reminiscent of those in some autistic children.

He notes that some children with autism do outgrow autistic behaviors by the time they reach their teen years. Could this be a parallel to the recovery of the foals with the maladjustment syndrome?



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Investigating possible links

A new group called the Comparative Neurology Research Group, consisting of veterinarians, physicians, epidemiologists and basic-science researchers, has formed to pursue further studies in this area. Madigan is working with researchers at the Stanford School of Medicine, exploring the mechanisms of post-birth transitions of consciousness related to neonatal care of infants.

Using data from the [foal](#) research, Pessah and Madigan are working with

environmental epidemiologist Irva Hertz-Picciotto at the UC Davis MIND Institute to investigate neurosteroids in children with varying degrees of autism, ranging from some developmental delay to full-spectrum autism.



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The researchers are exploring whether abnormal regulation of neurosteroids during the time around childbirth could be one of many factors that might contribute to autism and related neurodevelopmental disorders. A recent study has reported elevated levels of neurosteroids in

children with autism spectrum disorder.

Pessah and colleagues will be looking to see whether there are alterations in blood levels of certain neurosteroids that may serve as a marker for the disorder. They caution, however, that the relationship right now is just a theory that remains to be validated or disproven.

Provided by UC Davis

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