Objective. Nociceptive neuronal circuits are formed during embryonic and postnatal times, so insult during these periods may result in long-term alterations to pain circuitry via synaptic plasticity. One possible long-term result of plasticity is central hyperexcitability, which is suspected to be involved in chronic headache. This study aimed to establish whether there is an association between early pain experiences and the experience of migraines in later childhood.

Methods. In a retrospective study, we examined the charts of 280 pediatric migraineurs at the Division of Pediatric Neurology at Robert Wood Johnson Medical School and documented their perinatal history and migraine characteristics.

Results. Analysis revealed that there was a significant relationship between patients who had been in the NICU at birth and the type of pain medication prescribed when compared with patients who had not been in the NICU ($\chi^2$ test, $\chi^2 = 23.304; N = 30,250$). Findings also suggested that pediatric migraine patients who had been in the NICU at birth had a significantly earlier age of onset of their migraines ($\chi^2 \pm SD = 7.83 \pm 3.23; N = 30$) when compared with patients who did not remain in the NICU ($\chi^2 \pm SD = 9.68 \pm 3.57; N = 250$; Kolmogorov-Smirnov Test, $\chi^2 = 10.699$).

Conclusion. On the basis of these findings, we speculate that pain experience as a neonate, through neuronal plasticity and resulting central hyperexcitability, can alter the later experience of pain. However, this observational study cannot validate these links. Other potential explanations that work either synergistically or alone include other forms of stimulation and greater parental vigilance that may occur when neonates spend time in the NICU. This study would prompt additional development of a larger prospective study to establish a link between early pain experience and subsequent pain syndromes and also future investigation into the treatment of pain in neonates as a preventive measure for avoiding long-lasting neuronal alterations. Pediatrics 2005; 116:e555–e558. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0454; migraine headache, NICU, pain.

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sure to drugs in utero. The other group of perinatal stressor that did not require stays in the NICU included prematurity, cesarean sections, forceps used at delivery, prolonged hospital stays as a result of neonatal jaundice, pyloric stenosis, meconium aspiration, and readmissions for other reasons. All of those who had no indication of any perinatal complications were placed together in the third category.

Headache Severity

Documented medication was used as a measure of migraine severity. Migraine frequency and pain intensity would be considered when prescribing medication, so the type of medication would be an appropriate measure of severity. The medications were categorized into 3 levels. Level 1 included all over-the-counter pain medications such as acetaminophen or ibuprofen. Level 2 included prescription abortive medications such as triptans. Level 3 were daily, prophylactic medication of various kinds. All patients were 5 years or older when prescribed these medications.

Statistical Analysis

Statistical tests were conducted to compare the 3 categories of patients for differences in headache characteristics. Differences were assessed by χ² analysis or Kolmogorov-Smirnov test. Statistical analysis was conducted using StatView.

RESULTS

With the data obtained from the patient charts, statistical analysis was done in an attempt to answer several questions that would establish whether there was a correlation between perinatal experiences and migraine characteristics among our migraine patients. As specified in Methods, patients were divided into 3 categories: those who had spent time in the NICU, those who had experienced some other form of perinatal stress, and those who did not experience any perinatal complications. The reasoning was that those who were in the NICU were expected to have experienced more painful, invasive procedures, such as frequent heel sticks and venipuncture for blood collection, intubation, gavage tubes for feeding, placement and removal of electrodes for monitoring vital signs, surgery, and so forth, when compared with the other 2 groups. One would expect that other perinatal stressors might be more painful than no complications at all but that the pain would still be less than that of those who were in the NICU, so we first examined whether differences existed between those who had experienced some other form of perinatal stress and those who did not experience any perinatal complications. We found no significant differences between these 2 groups on any of the headache characteristics documented and therefore on subsequent analysis grouped these 2 groups, NOT NICU, in a comparison against the NICU group.

Medication

There was a significant relationship between patients who had been in the NICU at birth and level of pain medication compared with patients who had not been in the NICU ($\chi^2$ test, $\chi^2 = 23.304; P < .0001; N = 30$; see Fig 1). Overall heterogeneity is attributable to deviation from expectation in the relationship between patients who had been in the NICU and level 3 pain medications ($\chi^2$ test, $\chi^2 = 14.769; P < .01$). Thus, children who had been in the NICU at birth received a significantly higher level of pain medication than those who had not been in the NICU at birth.

Age of Onset

Pediatric migraine patients who had been in the NICU at birth had a significantly earlier age of onset of their migraines ($\chi^2$ ± SD = 7.83 ± 3.23; $N = 30$) when compared with patients who did not remain in the NICU ($\chi^2$ ± SD = 9.68 ± 3.57; $N = 250$; Kolmogorov-Smirnov Test, $\chi^2 = 10.699; P < .01$; see Fig 2).

Gender and Family History

Previous studies suggest that both gender and inheritance have an effect on migraines. It should be noted that childhood epidemiology is somewhat different from after puberty. Girls are affected more often than boys after puberty, and genetic predisposition to migraines is likely with a positive family history. Therefore, we examined whether either of these other predisposing characteristics was responsible for the effect of severity of headaches in patients who had been in NICU. Within the NICU group, there was no significant difference in the level
of medication required ($\chi^2$ test) or the age of onset of migraines (Kolmogorov-Smirnov test) between the genders or between those with and without a positive family history. This establishes that the effects found in the NICU group cannot be attributed to these other predisposing factors and supports that they are likely attributable to the NICU experience.

DISCUSSION

Our analysis shows that patients who remained in the NICU had both an earlier age of onset of their migraines and a significantly higher likelihood of being treated with a stronger, prophylactic, daily medication when compared with the other patients of this study. These results are consistent with previous observations that early painful experiences alter the developing nociceptive pathway via synaptic plasticity, which ultimately leads to a modified pain pathway that is capable of altering long-term pain experiences.\(^4\,\,^8\) Insult during embryonic and postnatal times in the form of needle pricks has been found to alter pain circuitry and subsequent pain response in rat pups for the long term.\(^4\,\,^{14}\) Additional evidence from studies on rats and rhesus monkeys indicates that a stressful perinatal event can have long-term effects on hippocampal development and stress behavior.\(^9\,\,^{15-17}\) Apart from the multitude of animal models, recent work on humans has provided evidence for developmental plasticity in the neonatal brain and suggests that painful experience in human neonates may alter neuronal and synaptic organization in the long term.\(^4\,\,^{18}\) Although these previous studies provide evidence for the long-term impact of early pain experience, the direction of the alteration has been conflicting. Some have found that early painful experiences lead to increased pain sensitivity in childhood, whereas others have found decreased pain sensitivity.\(^4\) This study falls in line with clinical studies that have found accentuated pain responses to vaccination in children who have had unanesthetized circumcision\(^1\) and instrumental delivery,\(^19\) suggesting central hyperexcitability. It also agrees with other observational studies on prematurely born adolescents who have been found to have lower tenderness thresholds and more tender points than full-term matches, suggesting that they may be more prone to developing pain syndromes.\(^20\)

Research has revealed that the synapse, which is the main site of communication between neurons, is the key substrate for these activity-induced changes.\(^21\) Long-term alterations in the structure and function of synapses, long-term synaptic plasticity, are crucial to the fine-tuning of the developing nervous system and to the storing and processing of the mature nervous system.\(^21\) The “use it or lose it” process of nociceptive development refers to the process in which synaptic connections are strengthened when pre- and postsynaptic activity is correlated and are otherwise weakened and eliminated. The mechanisms that elicit hyperexcitability have been categorized as 3 distinct forms: activation, modulation, and sensitization of peripheral terminal nociceptors and the central sensitization of nociceptive synaptic transmission. Modifications of the presensory neurons and pain transmission neurons are “long-lasting alterations in the expression of transmitters/receptors/ion channels or in the structure, connectivity, and survival of neuron, such that the system is grossly modified, distorting its normal stimulus-response characteristics.”\(^22\) It is believed that the resulting central hyperexcitability is considered the core phenomenon in patients with chronic pain.\(^23\)

Migraines are believed to be caused by neuronal events in nerve and chemical signals that cause these vessels to dilate or constrict. When these blood vessels expand and contract, the resulting changes in pressure produce pain.\(^24\) The process results in trigeminal sensitization as well as inflammation with subsequent release of neuropeptides and peptides.\(^25\) Because these synapses of nociceptive pathways are established and strengthened early in the NICU patients,\(^2\) the pain pathways are prepared and wired so that pain may develop sooner and stronger in severity.

Although our findings are consistent with the claim that pain experience as a neonate, through neuronal plasticity and resulting central hyperexcitability, can alter the later experience of chronic pain, this observational study cannot validate these links. Potential explanations that work either synergistically or alone include other forms of stimulation and greater parental vigilance that may occur when neonates spend time in the NICU. Although it cannot be controlled for, the group who remained in the NICU may be more susceptible to vulnerable child syndrome, whereby the parents believe that their child is more vulnerable to illness or injury than the typical child.\(^26\) These parents may also be more sensitive to their child’s illnesses and be more likely to seek treatment.

Additional limitations include the lack of detailed data such as length of stay in the NICU and number of procedures performed, which could possibly affect the severity of future migraines. Furthermore, other factors that are known to be accepted risks for future migraines, such as intracranial bleeds and central nervous system infections in childhood regardless of NICU stay, were present; 1 patient in the NICU had intracranial bleeding, and 5 had sepsis. However, sizes of these subsets were too small for analysis. Results from this study suggest that more detailed research should examine factors such as length of stay, reasons for stay, and procedure performed and examine subsets of children with problems that are known possibly to induce future migraines, such as intracranial bleeds or central nervous system infections, while recognizing that childhood epidemiology is somewhat different from after puberty.

We have not found evidence of the suggested theory but provide it as an explanation for our findings. The implications of this study would prompt additional investigation into the assessment and treatment of pain in neonates as a preventive measure for avoiding long-lasting neuronal alterations. We hope...
that this study will be used to develop a larger, prospective study to establish a link between early pain experience and subsequent pain syndromes, as well as allow grounds for the follow-up of NICU patients and additional investigation into disease mechanisms.

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