Younger Age at Onset Is Associated With Worse Long-term Behavioral Outcomes in Anti-NMDA Receptor Encephalitis

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Abstract

Background and Objectives
Anti-NMDA receptor encephalitis (anti-NMDARE) is one of the most common causes of encephalitis. It typically presents in adolescence and young adulthood, but little is known about its potential long-term consequences across the lifespan. Adaptive behavior describes an individual’s ability to respond and adapt to environmental demands and unanticipated changes in daily routines. In this study, we evaluate the relationship between features from clinical presentation, including age, and long-term adaptive behavior in participants with anti-NMDARE.

Methods
Cross-sectional informant-reported data were collected between 2017 and 2019 from 41 individuals/caregivers of individuals with anti-NMDARE treated at 3 major academic hospitals. Neurologic disability was assessed by record review using the modified Rankin Scale (mRS). Functional outcomes were assessed using the validated Adaptive Behavior Assessment System, Third Edition (ABAS-3).

Results
The mean age at the time of study enrollment was 23.4 years (SD 17.0 years), and the mean time from symptom onset to study enrollment was 4.0 years. Seventeen participants were aged <12 years at symptom onset, 19 participants were aged 12–30 years, and 5 participants were aged >30 years. Mean ABAS-3 scores at study enrollment for all participants were in the average range (mean general adaptive composite standard score 92.5, SD 18.7). Individuals aged <12 years at symptom onset had lower mean ABAS-3 scores and were in the below average range compared with those aged 12–30 years at symptom onset, whose mean scores were in the average range (87 vs 99, p < 0.05). Similar differences were seen in 3 of the individual subscales (functional academics, health and safety, and self-care). There were no significant differences in mRS scores between age groups (p > 0.05).

Discussion
Although anti-NMDARE is associated with an overall favorable outcome, younger age at onset associates with worse long-term adaptive behavior despite no differences in neurologic disability. These findings suggest that the disease may have distinct consequences on the early developing brain. Future studies should evaluate behavioral recovery and quality of life after anti-NMDARE and identify additional factors associated with differential recovery.
Anti-NMDA receptor encephalitis (anti-NMDARE) is now recognized as the most common identified cause of encephalitis in children and young adults, accounting for 40% of cases with an identified etiology and more common than any individual viral etiology. The disease manifests as subacute behavioral change or cognitive dysfunction often accompanied by reduced consciousness, speech dysfunction, seizures, movement disorder, and autonomic instability.

Recent literature has focused on advancing understanding of the long-term outcomes of individuals with anti-NMDARE. Although patients typically have dramatic and frequent improvement in motor disability, studies have also noted specific deficits in cognition, behavior, and psychosocial well-being, as well as substantial caregiver burden, years after initial presentation. Clinical features at the time of presentation that have been associated with poorer long-term outcomes include requirement for intensive care unit (ICU) admission and longer time between diagnosis and treatment initiation.

In this study, we aimed to evaluate long-term behavioral function in individuals with anti-NMDARE with focus on adaptive behavior, the ability to complete age-expected tasks in everyday environments. Adaptive behavior is a valuable outcome that encompasses functional outcomes in a real-world setting beyond what can be measured in performance-based testing. Furthermore, we investigated the association between features of their clinical presentations and long-term outcomes, in particular the role of age at symptom onset, based on earlier observations at a single institution of worse outcomes in those with symptom onset in childhood.

Methods

Study Participants
Children (aged <18 years) and adults (aged ≥18 years) treated for anti-NMDARE at the Johns Hopkins Hospital, Hospital of the University of Pennsylvania, and Children’s Hospital of Philadelphia from July 1, 2005, until June 30, 2015, were invited to participate in this study. At the Johns Hopkins Hospital, participants were identified based on chart review of all individuals with a billing diagnosis of encephalitis as part of a prior study. At the Hospital of the University of Pennsylvania and Children’s Hospital of Philadelphia, participants were identified through a preexisting clinical registry of all individuals with autoimmune encephalitis. At each site, chart review by a neurologist with expertise in autoimmune neurology (A.Y. and E.G.-L.) confirmed that individuals invited to participate in this study met the diagnostic consensus criteria for anti-NMDARE. As this study aimed to assess long-term outcomes, it was also required that at least 1 year had passed from the date of diagnosis to the date of study enrollment. Eligible participants (if younger than 18 years, participants’ legal guardians were contacted by telephone and asked to consent to participation in a structured telephone interview for this study.

Standard Protocol Approvals, Registrations, and Patient Consents
The study was approved by the institutional review boards at each site, and verbal informed consent was obtained and documented from all participants aged 18 years or older. For participants younger than 18 years, verbal informed consent was obtained and documented from their guardian. Verbal assent was also obtained and documented for children aged 8 years or older.

Clinical Data Collection
After consent was obtained, the following information was extracted from participants’ medical records: demographic details, symptoms and signs at initial presentation, diagnostic test results, immunotherapy administered, and clinical findings at hospital discharge and last follow-up with a neurologist.

Assessment of Adaptive Behavior, Neurologic Disability, and Neuropsychiatric Symptoms
The Adaptive Behavior Assessment System, Third Edition (ABAS-3), was administered. The ABAS-3 is a standardized age-normalized neurobehavioral rating scale of over 200 items for individuals from early infancy to adulthood, which assesses development, behavior, and cognitive abilities. Scores on these subscales are summed and normalized to the standardization sample to generate a general adaptive composite (GAC) standard score, which comprises 3 domain standard scores (conceptual, social, and practical). The conceptual domain comprises the communication, functional academics, and self-direction subscales. The social domain comprises the leisure and social subscales. The practical domain comprises the community use, home living, health and safety, and self-care subscales. Child forms of the test include a stand-alone motor subscale, and adult forms of the test include a stand-alone work subscale. Neither the motor nor work subscales are included in the domain or composite standard scores.

ABAS-3 GAC and domain standard scores are standardized to an average of 100 and SD of 15. Scores of 90–109 are classified average. Scores of 110–119 are classified above average, and 120 and above high. Scores of 80–89 are classified below average, 71–79 low, and 70 and below extremely low. For children (aged <18 years), parents or other caregivers completed the age-appropriate form for children (0–5 years or
Scores for modified Rankin Scale (mRS), a motor disability scale with scores ranging from 0 for no symptoms to 6 for death, were assigned independently by 2 raters (A.Y. and E.G.-L.) based on documentation in medical records. In the event of a discrepancy, scores were adjudicated to consensus. Each participant was assigned a score at hospital admission, hospital discharge, and last neurology follow-up. A score at study enrollment was also determined based on the structured telephone interview. As has been done in other studies of autoimmune encephalitis, a good score was defined by mRS score 0–2 and a poor score by mRS score 3–6. Participants were also asked to respond yes or no to whether they were currently experiencing neuropsychiatric symptoms in multiple domains including fatigue, emotional lability, short-term memory, and concentration.

Statistical Analyses
Statistical analyses were performed using STATA software version 14 (College Station, TX). The χ² and Fisher exact tests were used to test for associations between categorical variables, and 2-sided t tests were used to evaluate differences in means for continuous variables. p Value < 0.05 was considered significant.

The individual effects of participant and clinical factors on each outcome measure (ABAS-3 GAC standard score and mRS score at study enrollment) were tested with simple regression analyses, and the combined effects of multiple participant and clinical factors, adjusting for potential confounders, were tested in multiple regressions analysis. Examined participant and clinical factors included age at symptom onset, sex, percentage of White participants, seizure presence, tumor presence, requirement for ICU admission, immunotherapy administered (first-line treatment defined as steroids, plasma exchange, and/or IV immunoglobulin vs second-line treatment defined as rituximab and/or cyclophosphamide), and time interval from symptom onset to study enrollment. Given the cohort size, analyses for smaller subgroups were not performed.

Age at symptom onset was initially evaluated as a continuous variable. Subsequently, based on prior literature and examination of the distribution of data within this cohort, age at symptom onset was subsequently categorized as the following: <12 years (presumed prepubertal), 12–30 years (presumed postpubertal age through young adulthood), and >30 years (older adulthood).

Data Availability
The data that support the findings of this study can be made available by the corresponding author on request.

Results
Participant Characteristics and Clinical Profiles
A total of 41 participants with anti-NMDARE were enrolled in this study (eFigure 1, links.lww.com/NXI/A731). Thirty (73%) were female sex, and the mean age at the time of study enrollment was 23.4 years (SD 17.0 years). The mean time from symptom onset to study enrollment was 4.0 years (SD 2.4 years).

Nearly all participants had an mRS score of 3–5 on admission (some dependence on others for age-expected tasks; 39/41, 95%), and 21/41 (51%) required ICU admission during their acute hospitalization. No individual had a prior history of herpes simplex virus encephalitis. All individuals received immunotherapy (24% first-line only; 76% first-line and second-line). Additional details regarding participant characteristics and clinical profiles are displayed in Table 1.

Categorization of Age at Symptom Onset
Seventeen participants were aged <12 years at symptom onset, 19 participants were aged 12–30 years, and 5 participants

<table>
<thead>
<tr>
<th>Table 1 Participant Characteristics and Clinical Profiles</th>
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<tbody>
<tr>
<td>Number Percentage</td>
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<td>-------------------</td>
</tr>
<tr>
<td>Age at symptom onset (y)</td>
</tr>
<tr>
<td>Age at study enrollment (y)</td>
</tr>
<tr>
<td>Follow-up duration (y)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Tumor present</td>
</tr>
<tr>
<td>Immunotherapya</td>
</tr>
<tr>
<td>First line only</td>
</tr>
<tr>
<td>First and second line</td>
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<tr>
<td>Intensive care unit required</td>
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<tr>
<td>mRS score at admission</td>
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<tr>
<td>mRS score 0</td>
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<tr>
<td>mRS score 1</td>
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<td>mRS score 2</td>
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<td>mRS score 3</td>
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<td>mRS score 4</td>
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<td>mRS score 5</td>
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<td>mRS score 6</td>
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</tbody>
</table>

Abbreviation: mRS = modified Rankin Scale.

a First-line treatment = steroids, plasma exchange, and/or IV immunoglobulin. Second-line treatment = rituximab and/or cyclophosphamide.
were aged >30 years (eTable 1, links.lww.com/NXI/A731). Comparing participants aged <12 years and those aged 12–30 years, there were no differences seen in sex, percentage of White participants, presence of seizures, presence of tumor, requirement for ICU admission, mRS score at admission, or time interval from symptom onset to study enrollment. However, there was a difference in immunotherapy administered; participants aged <12 years were more likely to receive first-line treatment only compared with those aged 12–30 years (8/17 vs 2/19, p = 0.02). Given the low representation of individuals aged >30 years, similar demographic comparisons with this age group were not performed.

Adaptive Behavior, Neurologic Disability, and Neuropsychiatric Symptoms at Study Enrollment

On the ABAS-3 completed at the time of study enrollment (Table 2), mean standard scores of the GAC for all participants in this study were in the average range (mean GAC standard score 92.5, SD 18.7). Twenty-five participants scored in average (n = 16), above average (n = 6), or high (n = 3) ranges. Fifteen participants scored in the below average (n = 6), low (n = 4), or extremely low (n = 5) ranges.

### Table 2: Adaptive Function, Neurologic Disability, and Neurobehavioral Features at Study Enrollment

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td><strong>ABAS-3 standard score (n = 40)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General adaptive composite</td>
<td>92.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Conceptual domain</td>
<td>91.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Social domain</td>
<td>95.4</td>
<td>17.0</td>
</tr>
<tr>
<td>Practical domain</td>
<td>93.1</td>
<td>18.6</td>
</tr>
<tr>
<td><strong>mRS score at study enrollment (n = 40)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS score 0</td>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>mRS score 1</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>mRS score 2</td>
<td>10</td>
<td>25</td>
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<tr>
<td>mRS score 3</td>
<td>3</td>
<td>7.5</td>
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<tr>
<td>mRS score 4</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>mRS score 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mRS score 6</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Fatigue (n = 39)</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Emotional lability (n = 39)</td>
<td>19</td>
<td>46</td>
</tr>
<tr>
<td>Memory difficulties (n = 39)</td>
<td>17</td>
<td>41</td>
</tr>
<tr>
<td>Concentration difficulties (n = 39)</td>
<td>16</td>
<td>39</td>
</tr>
</tbody>
</table>

These findings were corroborated by assessment of neurologic disability, on which 35 participants (35/40, 88%) had a good outcome (mRS score of 0–2) at the time of study enrollment. This percentage was higher than at the time of initial hospital presentation (2/40, 5%; p < 0.0001), indicating that clinical improvement occurred in the time between initial presentation and study enrollment. At the time of study enrollment, 30 participants (30/39, 77%) endorsed at least one of the following persistent neuropsychiatric symptoms: fatigue (27%), emotional lability (46%), memory difficulties (41%), or concentration difficulties (39%).

Factors Associated With Adaptive Behavior Outcomes

In individual comparative analyses, ABAS-3 GAC standard scores at study enrollment did not differ based on race (White vs non-White), presence of seizures, presence of tumor, requirement for ICU admission, immunotherapy administered, ABAS-3 rater (self vs parent/caregiver), or time interval from symptom onset to study enrollment (eTable 2, links.lww.com/NXI/A731). Of interest, male participants had lower scores in comparison to female participants (p < 0.01).

The relationship between age at symptom onset and ABAS-3 GAC standard scores was examined (Figure 1, eFigure 2, links.lww.com/NXI/A731). However, given the low representation of individuals aged >30 years, they were excluded from these analyses. Among participants aged ≤30 years, those aged <12 years at symptom onset had lower ABAS-3 GAC standard scores and were in the below average range compared with those aged 12–30 years at symptom onset, who scored in the average range (87 vs 99, p < 0.05; Figure 2 and eTable 3, links.lww.com/NXI/A731). Similar differences were seen in 3 of the individual subscales (functional academics, health and safety, and self-care). Analysis was repeated after removing cases that were outliers across any of the domains, and this resulted in even more striking differences in scores between the age groups. Analyses coexamining the effect of age group and treatment received on outcomes were not performed because of sample size limitations.

Factors Associated With Neurologic Disability and Neuropsychiatric Symptoms

As noted in eTable 4, links.lww.com/NXI/A731, there was no association between age at symptom onset and mRS scores at study enrollment (p = 0.17), accounting for duration of follow-up, in participants aged 0–30 years. Likewise, there was no difference seen in mRS scores at study enrollment between participants aged <12 years and participants aged 12–30 years (p = 0.17). Furthermore, no associations were seen between age at symptom onset and current fatigue, short-term memory difficulties, and concentration difficulties at study enrollment. Individuals with emotional lability at study enrollment appear to have had an older age at symptom onset than those without emotional lability (p = 0.04); however, this is no longer the case when applying a correction for multiple comparisons (eTable 4, links.lww.com/NXI/A731).
Discussion

This study explores adaptive behavior outcomes after anti-NMDARE and demonstrates that although overall outcomes on this domain appear to be favorable, differences are seen by age such that younger children appear to have worse outcomes compared with adolescents and young adults. Long-term outcomes after anti-NMDARE appear to be favorable overall, as suggested by the fact that the average adaptive behavior score for participants in this study falls in the average range. Through use of a standardized age-normalized rating scale, adaptive behavior assesses an individual’s ability to function independently and meet environmental demands. It has been demonstrated by our group\textsuperscript{13,17} and others\textsuperscript{18,19} that adaptive behavior and other outcomes following anti-NMDARE may be better than those following other forms of autoimmune encephalitis and infectious encephalitis. In this study, our findings regarding adaptive behavior are corroborated by examination of neurologic disability, for which we found that the majority of participants have good outcome (mRS score 0–2), akin to what has been found in other studies in this disease.\textsuperscript{4} Furthermore, less than 50% of participants...
reported ongoing difficulties with fatigue, emotional lability, memory difficulties, and concentration difficulties.

Despite overall favorable adaptive behavior outcomes, we demonstrate that children with anti-NMDARE had worse scores compared with those who experienced anti-NMDARE onset in adolescence or young adulthood. Of note, younger age at onset did not lead to a higher risk of neurologic disability as assessed using the mRS. This finding emphasizes the importance of evaluating aspects of daily performance beyond traditional measures of motoric and fine motor functioning. Although children’s outcomes were worse than those of adults, they did not, on average, fall into the ranges of low or extremely low. However, modest impairments in adaptive functioning can still affect quality of life at home, at school, and in the community.20 Our findings of worse adaptive behavior outcomes in younger children are supported by previous literature examining the effects of age at symptom onset on long-term neurologic disability, as measured by mRS scores. An early and pivotal study of treatment and prognostic factors for long-term outcomes demonstrated in analyses restricted to adolescents and children a relationship of improved odds of good outcome (defined as mRS score of 0–2) after 24 months of follow-up with increasing age.4 In a more recent meta-analysis of individual patient data of 1,550 cases, infants younger than 2 years (along with adults aged 65 years and older) were likewise observed to have a more than 3 times increased odds of poor outcome, defined as mRS score of 3–6 after a median follow-up of 12.0 months (range 0.5–268.0 months).21 Conversely, in a separate literature review and meta-analysis of 80 previously reported cases of children with anti-NMDARE, no association was found between age at onset and rates of incomplete recovery, defined as mRS score of 2–6, after a median follow-up of 12 months (range 1.3–54 months).22 Future research is required to determine whether pediatric-onset anti-NMDARE portends a higher likelihood of need for school and social supports. It will also be of value to quantify the effect of anti-NMDARE on family functioning, not just the acute effect experienced during the acute illness, but the longer-term effect.

Early-onset anti-NMDARE might have a greater effect in the context of the developing brain. It has been demonstrated that clinical recovery results from downregulation of B-cell production of anti-NMDAR antibodies, leading to restoration of NMDARs and subsequent reversal of impairment in NMDAR function.23 However, it is not clear that such restoration of NMDARs would lead to restoration of all activity of NMDAR-related networks in a developing brain. Furthermore, profound encephalopathy can occur for months in anti-NMDARE during periods of critical neural development in children. It is possible that the prolonged loss of environmental enrichment, such as missed school and socialization, during the acute periods of anti-NMDARE may in itself lead to impairment in neural networks underlying learning and development that would otherwise be normally developing. Such phenomena have been reported in studies of pediatric traumatic brain injury.24,25 Even subtle alterations of these developmental trajectories may lead to reductions in daily function and quality of life, which can have critical consequences in social and educational settings.

Another potential explanation may be a difference in clinical factors by age that may play a role in outcomes. Prior studies have demonstrated that requirement for ICU admission and longer time between diagnosis and treatment initiation4,10-11 are associated with poorer long-term neurologic disability outcomes in anti-NMDARE. Although no differences were seen in this study in rates of ICU admission, delays in treatment initiation were not able to be evaluated, as it was difficult to accurately ascertain this information in many patients who had been transferred from outside hospitals. Furthermore, fewer children did receive second-line treatment (defined as rituximab and/or cyclophosphamide) compared with adults in this study. This may reflect physician discomfort with the use of these medications in children, despite several studies indicating safety and efficacy in the pediatric population, as they are not approved by the United States Food and Drug Administration for pediatric use.26 Correspondingly, prior studies have demonstrated a decreased risk of relapse in individuals receiving second-line treatment as well as improved neurologic disability outcomes in those who received second-line treatment after failing first-line treatment.10

A final possibility is a difference in sociologic factors between children and adults. Although an adult’s independence in activities of daily living is typically self-motivated, a child’s independence occurs within the context of a family. Given the often severe and protracted course of anti-NMDARE, it is possible that parents remain guarded about the freedom and independence they afford to a child who is recovering from severe illness. Such imposed limitations would be reflected in many of the questions on the ABAS-3 (e.g., “makes simple meals that require no cooking” or “attends fun activities at another’s home”). This may contribute to the observed lower scores in children in comparison to adolescents and young adults (notably, in the domains of health and safety, and self-care). Although this phenomenon may affect adaptive behavior in this patient population, it, nonetheless, may still represent an important psychosocial consequence of this disease and an important dynamic to consider when counseling families. Relatedly, because both children and adults were included in this study, respondents to the ABAS-3 included both participants themselves and their primary caregivers. Our analyses did not identify differences in ABAS-3 scores between those who responded themselves and those for which a caregiver responded. However, as seen in studies of other conditions,27,28 it is possible that individuals with anti-NMDARE themselves may answer differently than the parents/caregivers responding on their behalf.

Adaptive behavior outcomes of older adults with anti-NMDARE were partially examined in this study. Five participants in this cohort were over the age of 30 years and, in fact, all 5 were over the age of 50 years. Given the small number of participants in this age group, they were excluded from subgroup analyses examining the role of age on outcomes. Although not specifically analyzed in this study, qualitatively, 2...
participants scored in the above average range and 3 participants in the below average range on the ABAS-3. Of interest, the 2 participants who scored well both had a tumor discovered; however, there were no other apparent differences between the 2 groups in the clinical variables collected. Other comorbidities, including reasons for neurodegeneration, were not evaluated. Future studies should look at a larger cohort of older participants with anti-NMDARE with appropriate healthy controls and extraction of comprehensive medical information to determine if and how outcomes in this age group differ from those of children, adolescents, and young adults.

This study across 3 subspecialty centers demonstrates that anti-NMDARE is associated with an overall favorable outcome, although younger age at onset associates with worse long-term adaptive behavior. Limitations include the retrospective identification of patients, which may have introduced the possibility of selection bias (e.g., the inclusion of a large children’s hospital as one of the 3 cohorts led to a relative abundance of children and adolescents in this study.) An additional limitation was the cross-sectional assessment of participants, which led to variabilities in factors such as time from symptom onset to study enrollment. Future work through prospective and larger studies will evaluate behavioral recovery and quality of life after anti-NMDARE and identify additional factors associated with differential recovery. This will enable the examination of the role of factors that could not be examined in this study due to inconsistent data availability such as time from symptom onset to immunotherapy initiation and MRI brain findings. Although this study included a sizeable cohort because of its multisite nature, larger studies are needed to examine other variables such as potential differences between the outcomes of very young children and older adults compared with those of adolescents and young adults. Ultimately, improved understanding of outcomes may have implications for clinical management and the design of interventional (both pharmacologic and nonpharmacologic) studies in this patient population.

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Dr. Panzer is deceased.

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