The Effect of Low-Dose Ketamine on Aberrant Behaviors in Children with ADNP Syndrome

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BACKGROUND

• Activity-dependent neuroprotective protein (ADNP) syndrome is caused by pathogenic variants in the ADNP gene that lead to haploinsufficiency of the activity-dependent neuroprotective protein.1
• Over 400 genes are regulated by ADNP and haploinsufficiency negatively impacts brain development, manifesting clinically as aberrant behavior, cognitive and language delays, attention deficits and hyperactivity, sensory seeking behaviors, anxiety, and sleep disturbance.2,3,4
• Ketamine is an NMDA receptor antagonist that, in low doses, induces overexpression of ADNP in animal models.5

Objectives:
To evaluate the safety of low-dose ketamine treatment in children with ADNP syndrome as well as its efficacy for improving aberrant behaviors.

Hypothesis:
We hypothesized that treatment with low-dose ketamine would have a beneficial effect in individuals with ADNP syndrome. To assess clinical outcomes, we used a variety of measures, including the Aberrant Behavior Checklist (ABC), a caregiver rating instrument developed for use in individuals with intellectual disability to assess the severity of aberrant behaviors across five subscales.6

METHODS

Participants:

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<th>N</th>
<th>Mean Age (SD)</th>
<th>N (%female)</th>
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<td>ADNP</td>
<td>10</td>
<td>9.49 (2.29)</td>
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Inclusion criteria for this open-label clinical trial:
• ADNP diagnosis based on clinical genetic testing
• Clinical Global Impression-Severity (CGI-S) score of 4 (moderately ill) or greater at screening

Study Visits:
This study included the following clinic visits for the collection of safety, tolerability, and efficacy measures:

- Day 1 (D1): Infusion Assessment
- Day 0 (D0): Baseline Assessment
- Week 1 (W1): Post-infusion Assessment
- Week 2 (W2): Follow-up Assessment
- Week 4 (W4): Final Assessment

Clinical Assessments:

Measures were collected pre-infusion (D0) and at four time points post-infusion (D1, W1, W2, W4). All participants were evaluated for drug safety and tolerability using physical examination, laboratory assessments, and vital signs which were monitored throughout the infusion and at all clinic visits.

The Systematic Longitudinal Adverse Events Scale (SLAES):
The SLAES was administered by the study physician at each time point to monitor the safety of the drug administration as the trial progressed.

The Aberrant Behavior Checklist (ABC):
The ABC was completed by the same parent at each time point to measure psychiatric symptoms exhibited across each time point. The ABC includes five domains: Irritability, Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech.

Analysis:
• A Wilcoxon signed-rank test was calculated for the differences in data distributions (change over time) from D0 to D1, W1, W2, and W4 to examine treatment effects. All tests of statistical hypotheses were done on the two-sided 5% level of significance.
• Since this was an initial proof-of-concept study, no adjustments were made for multiple comparisons in the reported p-values.

CONCLUSIONS

• We found that ketamine was well tolerated and no serious adverse events were reported.
• ABC results showed a significant decrease in four of the five subscales following ketamine treatment, suggesting overall improved aberrant behavior.
• The Inappropriate Speech subscale scores did not reflect improvement, likely because of the low verbal abilities of participants at baseline.
• This work suggests that low-dose ketamine is both safe for this cohort and potentially effective in reducing aberrant behaviors in children with ADNP syndrome.

Future Directions:
• Future studies will employ a randomized, placebo-controlled design and will study the effects of repeated ketamine dosing over a longer duration of time.
• Further studies will recruit more participants with ADNP syndrome to participate.

RESEARCHERS


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