A Study of Behaviors Associated with Fever in Children with Autism/PDD

Laura K. Curran[1,2], Stephen O. Crawford[2], Craig J. Newschaffer[2] and Andrew W. Zimmerman[1]

[1]Kennedy Krieger Institute, Baltimore, MD; [2]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

Background

Over the past few decades, parents and clinicians have reported that behaviors of children with autism tend to improve, sometimes rather dramatically, during febrile episodes. In our informal surveys at local autism society gatherings, approximately 30% to 40% of parents responded that they had observed marked improvements of their children's behaviors during fevers, particularly better language and social interaction. From a clinical setting, staff at New York University's Bellevue Psychiatric Hospital reported improved communicative speech, increased alertness, decreased withdrawal, increased verbal output and attempts to 'reach out' and communicate with adults (not previously observed) during episodes of fever (Sullivan et al, 1980). In particular, during an epidemic of viral upper respiratory infections on a ward with children with autism, NYU staff observed substantial behavior changes, including longer concentration spans and increased relations with adults and peers in children with temperatures of 102.0°F to 105.0°F. After the fever ended, most of the noted behavior improvements decreased toward baseline. It was suggested that these changes were related both to the physical illness as well as to the elevation in body temperature.

Recent advances in immunology and neuroscience are beginning to provide possible clues to neuro-immunological changes in the brain in autism. Fever leads to marked changes in the body and brain, and is likely to alter patterns of cytokines, neurohormones and intracellular signaling pathways that affect neuronal and synaptic functions that affect behavior. Therefore, behavioral changes during fever may provide opportunities to understand the neurobiological basis of autism.

In this study, we investigated behaviors during and after febrile episodes.

Methods

We conducted a prospective study between September 2002 and November 2003 of 109 children with ASD/PDD, ages 2-18 years, seen at a clinical facility between 1992 and 2002, or affiliated with one of two select autism groups. Of the 109 enrolled subjects, 40 acquired fevers during the study period. Behaviors were evaluated by their parents and objective observers using the Aberrant Behavior Checklist (ABC) at three time points:

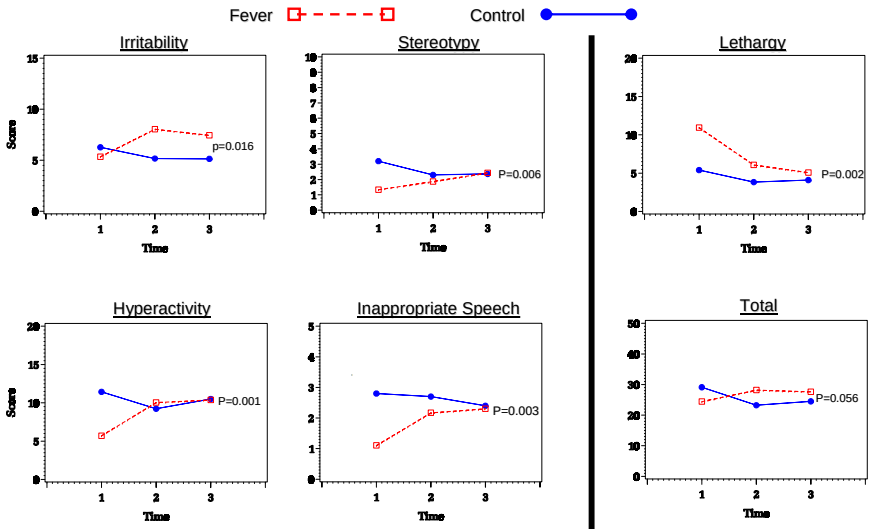
Time 1: During fever (body temperature ≥100.4 °F);
Time 2: When the fever was gone and the child was feeling better; and
Time 3: Once the child was fever-free for 7 days.

Control subjects were available for 30 of the 40 fever subjects. For each, one age-, sex- and language skills-matched control subject was selected from the list of ASD/PDD children who had not yet submitted data and were fever-free at the time. A parent of each control subject completed the ABC on three sequential days spaced according to the reported schedule of the febrile child.

For the main outcome measure, mean ABC scores for subject pairs were plotted and repeated-measures analysis of variance (RM-ANOVA) modeling was used to check for overall differences in behaviors between fevers and controls over time (n=30 matched pairs).

We then tested whether or not any observed association between fever and behavior change persisted after stratifying subjects by multiple third variables. In particular, we attempted to separate effects due to fever from effects attributable to underlying attendant illnesses or to treatments for the febrile illness.

Main Outcome Measure: Mean ABC Subscale Scores and *p-values* from Repeated Measures ANOVA (n=30 matched pairs)

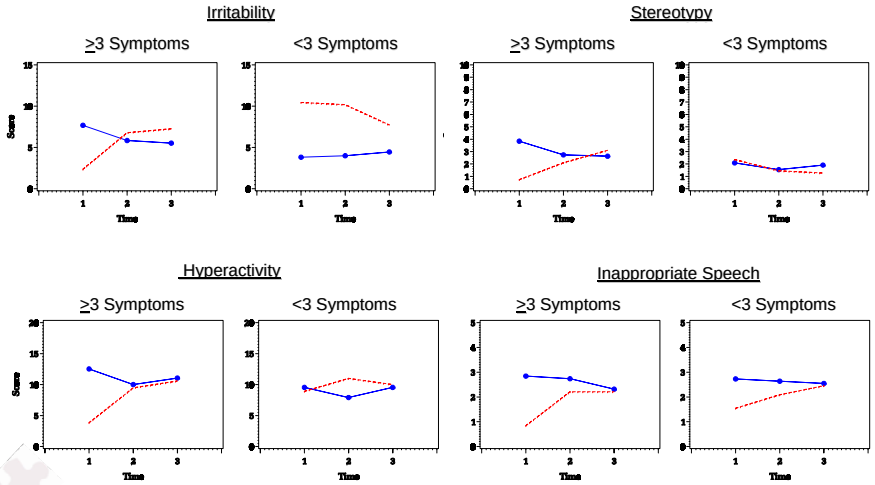


Higher scores indicate worse behaviors; therefore, a positive trajectory from Time 1 (fever onset) to Time 3 ("back to baseline") or a higher score at Time 3 than Time 1 suggests improvements associated with fevers.

The Total score represents the sum of the five subscale scores.

Investigating an Effect due to Illness: Stratification by Number of Symptoms Reported During Fever

Formal statistical testing for three-way interactions could not be conducted due to small within-stratum sample sizes.



Results

As shown in the six figures to the left, behavior improvements during fevers were statistically significant on the Irritability, Stereotypy, Hyperactivity, and Inappropriate Speech subscales (p<0.02). Per expectation, Lethargy subscale scores were worse at Time 1 (fever), and accordingly, the Total score, which represents the summation of the five subscales, showed less of a beneficial fever effect due to the opposing findings on the Lethargy subscale.

A closer look at all fever subjects revealed that 25 of 30 (83%) showed better behaviors during fever (considering the Irritability, Stereotypy, Hyperactivity and Inappropriate Speech subscales together). With regard to Inappropriate Speech in particular, improvements during fever were identified in 17 of 30 (57%) fever subjects. Of the fever "improvers", 22 of the 25 (88%) showed improvement on at least two subscales, and 15 of 25 (60%) showed improvement on at least three subscales.

In our limited sample, underlying attendant illness (as reflected in the number of symptoms reported at the time of fever onset) may have influenced the findings. As shown in the figures for the Irritability, Stereotypy and Hyperactivity subscales (below left), stratification of subjects by the number of reported symptoms reveals lower scores at Time 1 for "sicker" fever subjects (with 3 or more symptoms) that are not seen for the "less sick" fever subjects (with less than 3 accompanying symptoms). However, the effect from fever held for the Inappropriate Speech subscale, where we identified similar improvements during fever in both symptom groups.

Discussion

Our data suggest that fever may positively impact behaviors characteristic of autism, particularly inappropriate speech. Our findings exceeded estimates of improvements associated with fever as sampled in parent groups, and suggest a potentially important area for further research. The repeatability of a behavior phenomenon associated with fever may reflect a subgroup of patients who have specific underlying abnormalities in neurochemical pathways that may be genetically determined and modified during brain development. Unexpected behavioral improvements during fever in children with autism imply that potentially functional neural networks that are critical for language or social interaction might be able to respond to stimulation by "fever factors". These might include multiple cytokines, chemokines, growth factors and hormones that can affect intracellular signaling and improve neuronal and synaptic plasticity. Such factors may also be anti-inflammatory and capable of downregulating innate neuroinflammation that results from chronic microglial and astrocytic activation in the brain in autism (Vargas DL et al, 2005).

To our knowledge, this study is the first to investigate behavior changes associated with fever in children with ASD/PDD. It provides a strong study design to investigate a phenomenon that is only anecdotal to date. Perhaps the biggest limitation of the study was the modest response rate (2% of households responded to a mailed study packet). Larger, more controlled studies of this phenomenon are warranted. Additionally, further research is needed to define clinical aspects of fever in autism, as well as the cellular mechanisms that may suggest new approaches to treatment.

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