ARTICLE

Behaviors Associated With Fever in Children With Autism Spectrum Disorders

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ABSTRACT

OBJECTIVE. Clinical case reports have suggested that the behaviors of children with autism spectrum disorders may improve with fever. The purpose of this study was to investigate the effect of illness on behaviors of children with autism spectrum disorders. Understanding the role of fever, if any, may be informative regarding causative mechanisms of and treatment opportunities for autism.

METHODS. We conducted a prospective study of 30 children (aged 2–18 years) with autism spectrum disorders during and after an episode of fever. Parent responses to the Aberrant Behavior Checklist were collected during fever (body temperature ≥ 38.0°C/100.4°F), when fever had abated and the child was asymptomatic, and when the child had been fever-free for 7 days. Data were compared with those collected from parents of 30 age-, gender-, and language skills–matched afebrile children with autism spectrum disorders during similar time intervals.

RESULTS. Fewer aberrant behaviors were recorded for febrile patients on the Aberrant Behavior Checklist subscales of irritability, hyperactivity, stereotypy, and inappropriate speech compared with control subjects. Per expectation, lethargy scores were greater during fevers, and all improvements were transient. Data from patients with fever were stratified on variables related to illness severity. In the majority of these subgroup comparisons, the data suggested that effects from fever persisted in the less sick patients as well as in those with more severe illness.

CONCLUSIONS. We documented behavior change among children with autism spectrum disorders during fever. The data suggest that these changes might not be solely the byproduct of general effects of sickness on behavior; however, more research is needed to prove conclusively fever-specific effects and elucidate their underlying biological mechanisms (possibly involving immunologic and neurobiological pathways, intracellular signaling, and synaptic plasticity).

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Key Words
autism spectrum disorders, autistic disorder, fever, behavior, children

Abbreviations
ASD—autism spectrum disorder
PDD-NOS—pervasive developmental disorder not otherwise specified
ABC—Aberrant Behavior Checklist

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AUTISM SPECTRUM DISORDERS (ASDs), including autism or autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome are characterized by limited social interactions, deficits in verbal and nonverbal communication, and a restricted repertoire of activities and interests.[1] Because ASDs are behaviorally defined and diagnosed, studies of past and current behaviors are critical to increasing our understanding of this complex group of disorders. Observations of changes in behavior over time and factors that influence them, in particular, may offer suggestions for research strategies as well as insights about the affected children's underlying capabilities.

During an epidemic of viral upper respiratory infections on a ward with children with ASDs, staff at New York University's Bellevue Psychiatric Hospital observed changes such as longer concentration spans and increased relations with adults and peers in children with temperatures of 38.9 to 40.6°C (102.0–105.0°F).[2] In previous observations at Bellevue, behavioral improvements disappeared when the children recovered from the febrile illnesses, although it was noted that they often did not seem physically ill during the febrile episodes. It has been suggested that maximal improvements in autistic behaviors may occur at elevations of 1.5 to 2.5°C (2.7–4.5°F) in body temperature.[3]

In the past few decades, parents and clinicians have reported that behaviors of children with ASDs tend to improve, sometimes dramatically, during febrile episodes.[4–6] The degrees of fever required to evoke behavior changes in children with ASDs have varied among children and infections. Improvements have appeared before or soon after the onset of fever and have subsided within 1 to 3 days after the fever was gone. Furthermore, anecdotal reports suggest that effects that are stimulated by fever are not evoked by high ambient heat associated with a sauna, hot summer weather, or physical activity.

Fever is a complex adaptive response mediated by endocrine, autonomic, and behavioral responses organized by the brain in response to inflammatory stimuli.[7] Despite widespread occurrence of fever among all animals and centuries of studies in humans, the functional significance of fever remains uncertain, although it has been associated with enhanced immune function and survival from life-threatening infections.[8] Fever occurs commonly in childhood, usually associated with intercurrent bacterial or viral infections and accompanied by various sickness behaviors such as irritability and lethargy[9] but not improved behaviors as reported in children with ASDs.

The pathways that are involved in fever reflect elaborate interactions between the immune and nervous systems, as a result of multiple cytokines, neurohormones, and intracellular signaling pathways that affect neuronal and synaptic functions, as well as the child's behavior.[10] The rapid behavioral changes that are reported during fever in ASDs suggest that dysfunctional neural networks in ASDs might be nascent and potentially intact, and understanding the reasons for improvement during fever might provide insight to the neurobiological basis of ASDs.

The suggestion of a fever effect in ASDs is based on case reports and anecdotes. Given the biological plausibility and the potential implications for treatment opportunities, we undertook a formal study of behavior changes associated with fever in this population. This study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

METHODS

Participants

Study participants were predominantly recruited from the billing database (AS-400) of the Kennedy Krieger Institute (Baltimore, MD). Targeted searches of this database were performed to identify children who were aged 2 to 18 years and had *International Classification of Diseases, Ninth Revision* diagnoses of ASDs. Additional participants were identified from the Delaware Autism Program, a statewide public education program for children with ASDs, and the Autism Society of America, Chapter of East Tennessee, an autism community support and advocacy organization. Children in the Delaware Autism Program must meet the state of Delaware's criteria for an autism special education classification. Clinical diagnoses of children recruited from the Autism Society of America, Chapter of East Tennessee, were confirmed on enrollment. Children with genetic disorders (eg, fragile X syndrome, Down syndrome, Rett syndrome) listed on the enrollment questionnaire were excluded from the study. Families were informed that researchers were interested in behaviors when children have illnesses and when children are feeling well, but the study hypothesis (that behavior improves with fever) was concealed.

Eligible children (n = 103) were enrolled and followed prospectively for fever (Fig 1). For the majority (53%) of children, parents reported that their children had been assigned clinical diagnoses of autistic disorder, 32% reported diagnoses consistent with higher levels of cognitive and adaptive functioning (Asperger syndrome, high-functioning autism, or PDD-NOS), and parents of the remaining 15% listed diagnoses for which it was difficult to determine the extent of impairment (ASDs or PDDs). Information was also solicited on children's use of language to provide additional insight about impairment levels. As described next, the final analytic sample comprised 30 children who developed fever during the follow-up period and 30 control subjects who were matched on age, gender, and language skills. Table 1 presents characteristics of these study children.

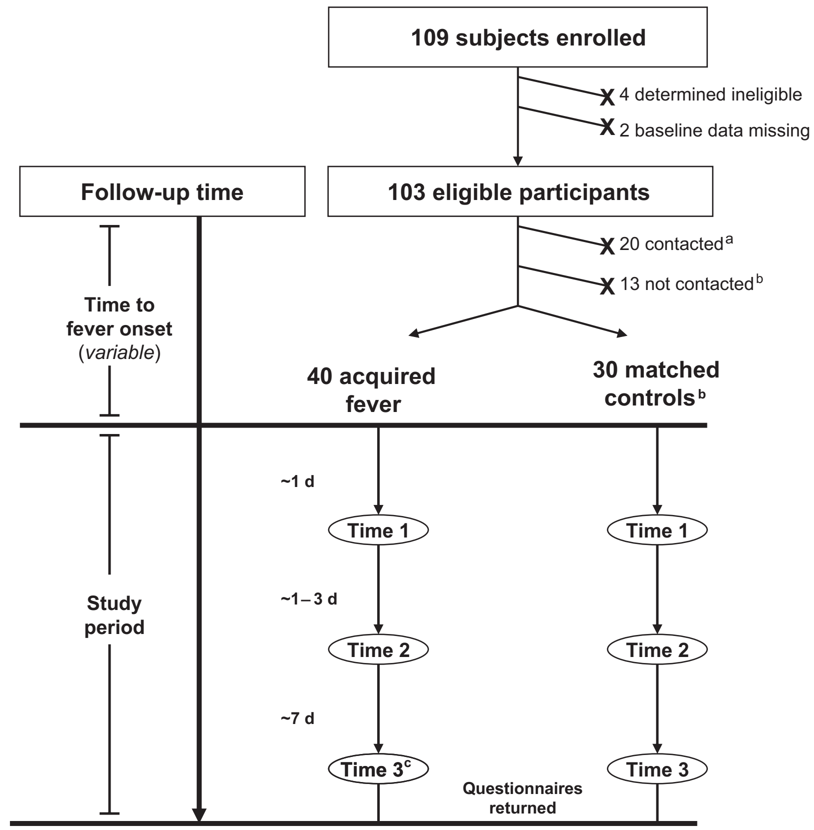

FIGURE 1
Participation flow. [a] Control data were requested from parent by telephone but not received; [b] families did not provide fever or control data, and they were not requested; [c] a control subject was selected after data were received from each fever subject.

Data Collection

Fever was defined as a body temperature of ≥ 38.0°C (100.4°F). Parents were provided with FeverScan (Digi-Temp, Glenview, IL) liquid crystal thermometer strips for use on the forehead. These were selected for distribution (by mail) because of their safety, convenience, ease of use, disposability, and noninvasiveness, but parents were instructed to use their preferred type of thermometer to monitor their children's temperatures prospectively at parents' convenience and when illness was suspected.

Once a fever was recorded, parents were asked to observe their child's behaviors carefully during the subsequent 24 hours and then to complete the first study questionnaire (time 1; described in "Questionnaire"). After time 1, parents were directed to mark when the fever had disappeared and the parent determined that the child was feeling better. Parents were asked to observe the child during the next 24 hours and then to complete the second copy of the study questionnaire at time 2. After time 2, parents were instructed to continue to monitor the child's temperature until 7 days without fever had accrued. At that point, parents were asked to complete the third and final copy of the questionnaire, based on the child's behaviors during a 24-hour observation period (time 3). This third time point effectively served as a "fever-free" measurement; data were collected when the child was unaffected by fever.

On completion of data collection on a child with fever, the list of eligible children who had not yet reported a fever was reviewed for a match by age (in 5 categories: 3–5, 6–8, 9–11, 12–14, and 15–18 years), gender, and language skills (fluent speech, simple phrases, single words, or no language). When an appropriate age match was not available within a gender category, the adjacent age categories were searched. When multiple eligible control subjects were identified, a random number was generated to select from among them.

Potential control subjects first confirmed that the child was afebrile over the past week. Then parents from control families were instructed to provide behavioral data during a time course identical to that of the patient with fever to whom they were matched. That is, if for a given patient with fever the intervals between time 1 and time 2 and time 2 and time 3 were 3 and 7 days, respectively, then parents of the matched control subject provided data with the same spacing. Independence was maintained between and within fever and control groups: selected afebrile children served as control subjects for only 1 case, and families who contributed data to 1 study group could not contribute to the other.

Questionnaire

The study questionnaire that parents completed at times 1, 2, and 3 was a slightly modified version of the Aberrant Behavior Checklist (ABC).[11] The ABC is a 58-item,

TABLE 1 **Demographic Characteristics of Study Participants (*N* = 103)**

Characteristic	Patients With Fever (*n* = 30)	Control Subjects (*n* = 30)	Nonmatched Patients With Fever (*n* = 10)[a]	Contacted (*n* = 20)[a]	Not Contacted (*n* = 13)[a]
Age, mean (SD), y[b]	7.4 (3.3)	8.8 (2.8)	5.6 (2.1)	7.8 (2.7)	11.4 (2.9)
Gender, *n* (%)					
Male	24 (80)	24 (80)	9 (90)	16 (80)	13 (100)
Female	6 (20)	6 (20)	1 (10)	4 (20)	0 (0)
Diagnosis, *n* (%)					
Autism	12 (40)	13 (43)	9 (90)	14 (70)	7 (54)
Asperger syndrome/high-functioning autism/PDD-NOS	13 (43)	11 (37)	1 (10)	4 (20)	4 (31)
ASDs or PDD	5 (17)	6 (20)	0 (0)	2 (10)	2 (15)
Developmental regression, *n* (%)					
Yes	11 (37)	10 (33)	4 (44)	12 (60)	4 (31)
No	14 (47)	16 (53)	5 (56)	8 (40)	8 (62)
Don't know	5 (17)	4 (13)	0 (0)	0 (0)	1 (8)
Language skills, *n* (%)					
Fluent	10 (33)	14 (47)	1 (10)	7 (35)	5 (38)
Simple phrases	14 (47)	9 (30)	5 (50)	9 (45)	3 (23)
Single words	4 (13)	4 (13)	2 (20)	1 (5)	1 (8)
None	2 (7)	3 (10)	2 (20)	3 (15)	4 (31)
Medication use, *n* (%)[c]					
None	12 (40)	12 (40)	6 (60)	13 (65)	4 (31)
SSRIs	7 (23)	8 (27)	2 (20)	1 (5)	4 (31)
Other psychotropic drugs[d]	13 (43)	16 (53)	3 (30)	7 (35)	9 (69)
Parents' perceptions of behavior change during fever, *n* (%)[e]					
No change	5 (17)	8 (27)	1 (10)	5 (25)	2 (17)
Changes somewhat	8 (27)	7 (23)	3 (30)	4 (20)	2 (17)
Definitely changes	17 (57)	15 (50)	6 (60)	11 (55)	8 (67)

SSRIs indicates selective serotonin-reuptake inhibitors.

[a] Sample size varies depending on the number of participants who answered the question.

[b] Based on age at time of fever onset and control selection (or age at enrollment for the not-contacted group).

[c] Some children used multiple medications.

[d] Includes non–selective serotonin-reuptake inhibitor antidepressants, antianxiety drugs, antipsychotic agents, mood stabilizers, anticonvulsant agents, and attention drugs.

[e] At baseline, parents were asked to inform if the child's behavior changes during 5 different scenarios (eg, fever, bath time) in ways other than "typical tiredness, getting upset, or irritated."

third-party informant scale that solicits information about behavior severity using a 4-point scale. ABC subscales include irritability (15 items), lethargy (16 items), hyperactivity (16 items), stereotypy (7 items), and inappropriate speech (4 items). Individual items are summed to yield subscale scores, with higher scores suggestive of greater severity. Questions were also asked about symptoms that accompanied the febrile illnesses (eg, sore throat, congestion, headache, coughing, sneezing).

Analytic Methods

For each of the ABC subscale scores, repeated-measures analysis of variance modeling was used to check for differences in behaviors over time between patients with fever and control subjects who contributed data at all 3 time points. Analyses were repeated stratifying fever and nonfever pairs according to characteristics of the patients with fever. Markers of severity of illness were considered, including the height of the fever, the amount of lethargy recorded at time 1 (marked by lethargy subscale scores), and the number of symptoms that accompanied the fever. Use of fever/illness treatments, such as analgesics, antibiotics, or allergy medications, was also investigated. Data were unmatched to explore potential confounding and effect modification by gender, autism characteristics (specific diagnosis, history of developmental regression, language skills, and psychotropic drug use), and parents' a priori expectations of behavior change with fever. Because of limited within-stratum sample size, we did not perform formal statistical testing of 3-way interactions. Statistical analyses were performed by using SAS 9.1 (SAS Institute Inc, Cary, NC) and Intercooled Stata 8.0 (Stata Corp, College Station, TX).

RESULTS

Control subjects were slightly older than the patients with fever (mean age: 8.8 vs 7.4 years, respectively), consistent with the fact that younger children are more likely to contract fevers than older children (Table 1).[9] Patients with fever and control subjects had similar distributions among other variables, such as diagnosis, experience of developmental regression, and medication use. Of note, 17 (57%) of 30 parents of patients with fever and 15 (50%) of 30 parents of control subjects had reported at baseline (before assignment to the fever or the control group) that they had observed definite behavior changes during febrile episodes; however, qualitative information on the type of behavior change (eg, better or worse) expected with fever was not solicited.

Considering data from febrile patients only, 25 (83%) of 30 children with fevers had higher (worse) scores during fevers than during the time 3 fever-free measure on the lethargy subscale; however, a similar proportion, 25 (83%) of 30, showed fewer aberrant behaviors during fever on at least 1 of the other ABC scale domains, with 22 (88%) of these 25 children having fewer aberrant behaviors on at least 2 subscales and 16 (64%) of 25 on at least 3 subscales. Children with a diagnosis of autistic disorder were more likely to show fewer aberrant behaviors during fever than children with a diagnosis of PDD-NOS or Asperger syndrome, reflected by proportions of patients who had fever and improved on ≥2 subscales of 10 (83%) of 12, 7 (64%) of 11, and 1 (50%) of 2, respectively. With regard to the inappropriate speech subscale in particular, fewer aberrant behaviors were reported for 17 (57%) of 30 patients during fever than during the time 3 fever-free measurements. Of these 17 patients, only 4 (24%) had a diagnosis of autistic disorder; the group for whom less inappropriate speech was recorded during fever primarily consisted of patients with higher language skills (7 of 17 [41%] used fluent speech, and 8 of 17 [47%] used simple phrases, versus 2 of 17 [12%] who used single words only).

The results from the comparison of fever and control group data are shown in Fig 2, which displays mean ABC scores (95% confidence intervals) at each of the 3 time points. Time-by-group interactions from the repeated-measures analysis of variance were significant for all subscales (irritability, $P = .016$; lethargy, $P = .002$; hyperactivity, $P = .001$; stereotypy, $P = .006$; and inappropriate speech, $P = .003$). This suggests that the patterns over time within the fever group differed significantly from patterns over time for children with ASDs and without fever.

Stratified analyses of fever group patients (data not shown) indicated there were no marked differences in the patterns of mean irritability, hyperactivity, stereotypy, and inappropriate speech subscale scores among patients with higher (≥102.0°F) and lower fevers (100.4–102.0°F), suggesting that reduction of aberrant behavior during fever did not depend on the height of the fever. Similar findings were observed in the comparison between subject groups with higher and lower lethargy (defined as above and below the median lethargy subscale score at time 1, respectively), suggesting that reduction of aberrant behavior during fever also did not depend on the amount of lethargy measured at that time. Stratification by number of symptoms that accompanied fever did not yield as consistent results. Patients with ≥3 accompanying symptoms had better (lower) scores on the domains of irritability, hyperactivity, and stereotypy at fever (time 1) than did patients who had fever with <3 accompanying symptoms; however, similar reductions in the inappropriate speech subscale be-

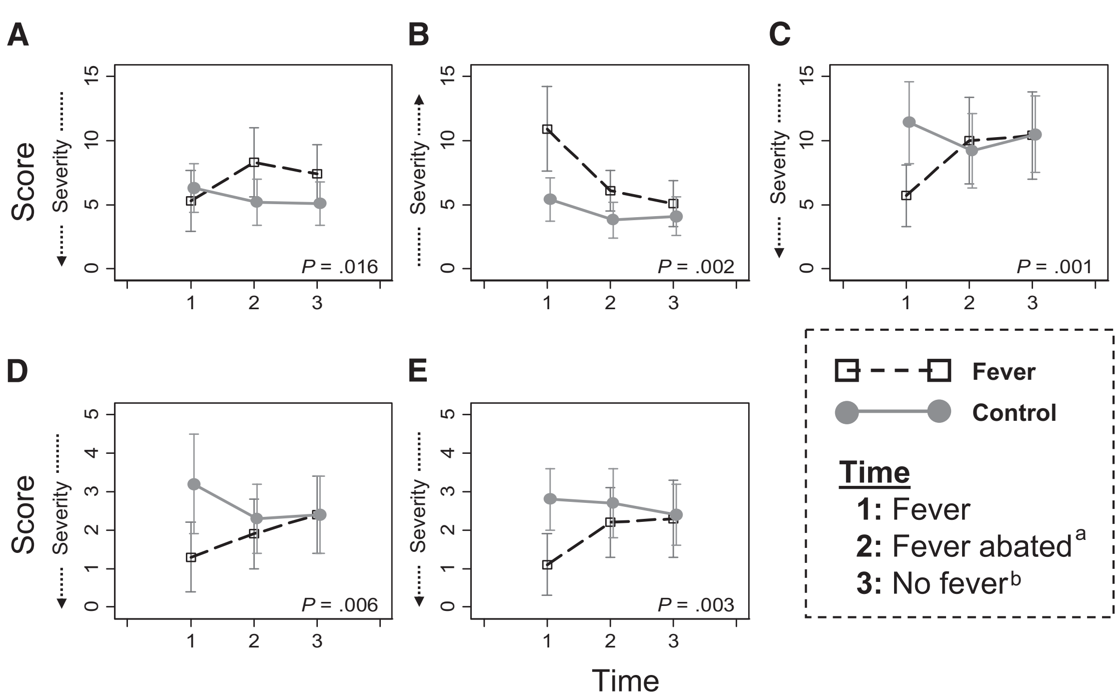

FIGURE 2
Mean ABC subscale scores across times 1, 2, and 3 and P values from repeated-measures analysis of variance (time × group interaction; $n = 30$ matched pairs). A, Irritability; B, lethargy; C, hyperactivity; D, stereotypy; E, inappropriate speech. Error bars represent 95% confidence intervals; arrows on the y-axis indicate increased or decreased severity of each behavior observed during fever. [a] Child was asymptomatic 1 to 3 days after fever; [b] ~1 week after time 2.

haviors at time 1 compared with time 3 were seen in both symptom groups. Additional stratified analyses did not reveal any marked differences in patterns of ABC subscales over time among patients with fever across groups defined by gender, diagnosis, presence of developmental regression, language skills, medication use, or parents' expectations of change during fever (as reported at enrollment). One analysis considered the use of analgesics, antibiotics, and allergy medications, and a second, separate analysis considered the use of selective serotonin reuptake inhibitors and other psychotropic drugs; however, neither showed differential effects during fever.

DISCUSSION

To our knowledge, this study is the first to investigate behavioral changes associated with fever in children with ASDs. Belief in the therapeutic value of fever for disorders such as epilepsy and melancholy dates back to Hippocrates and Galen.[12] In 1887, Wagner von Jauregg began inducing fever as therapy for psychoses,[13] using injections of tuberculin, and later malaria, which led to the widespread use of fever therapy for neurosyphilis in the 1920s, until the advent of penicillin in the mid-1940s.[12,14] Farrell et al[15] reported functional improvements and decreased periodic complexes on electroencephalograms in patients with subacute sclerosing leukoencephalitis during fever and with increased body temperature, which they attributed to modified synaptic activity.

We observed fewer aberrant behaviors during fever on the ABC domains of irritability, hyperactivity, stereotypy, and inappropriate speech. To explore whether these behavioral changes were related to general behavioral suppression associated with illness, as opposed to a specific response to fever, we conducted stratified analyses to determine whether changes were more pronounced among those with higher fever, more lethargy during fever, or more accompanying nonfever symptoms. The majority of these subgroup comparisons suggested that behavior change was not a function of illness severity. However, for 3 ABC subscales, the difference between time 1 behavior (during fever) and time 3 behavior (1 week after fever) did seem to be limited to the subgroup with higher nonfever symptoms, suggesting a role for overall level of illness. Yet the fact that other stratifications did not reveal this heterogeneity of effect and that the inappropriate speech subscale consistently was affected by fever in all lower illness subgroups created indicates that biological mechanisms that are related to fever and could potentially have an impact on behavior should be considered further.

Explanations for the behavioral effects of fever in ASDs may involve interactions between systemic immune responses and neurobiological mechanisms of cortical and neuronal function,[10] including (1) neurobiological effects of selected proinflammatory[16] and/or anti-inflammatory cytokines, which have been found to be increased in cerebrospinal fluid (in the absence of fever) and postmortem brain tissue of individuals with autism[17] and may be generated during different phases of responses to fever, (2) modification of neuronal and synaptic function secondary to variations in body temperature that influence neural conduction velocities or synaptic transmission,[18] (3) modification of dynamic neural networks as a result of changes in cellular signal transduction and gene transcription that regulate synapse formation and function,[19] (4) increased production of other stress-related proteins, such as heat-shock proteins, during fever that might modify energy consumption and mitochondrial activity,[20] and (5) stimulation of the hypothalamic-pituitary-adrenal axis leading to modifications of neurotransmitter production and interaction.[21] Should any of these mechanisms be proved to effect behavior changes in individuals with ASDs, this would stimulate research on potential treatments focused on these pathways.

This study has limitations. Although subgroup comparisons suggest some specificity of the fever effect, the study did not include a comparison group of children with nonfebrile illnesses. Our measures of behavior were based solely on parent reports; these data are subject to information biases. Because symptom data were collected prospectively, however, recall bias, a major source of information bias, was likely limited. Future studies may benefit from including independent raters (eg, teachers) or using videos to limit subjective misclassification of changes in behavior. Selection bias is also possible because a small fraction of eligible families from recruitment sources participated. Just more than half of families in the final analysis sample reported a priori that they thought that fever affected their children's behaviors, and this proportion may be higher than that of the general population of parents of children with ASDs, yet among families who experienced fever during the study period, behavior change documented prospectively was similar in those with and without the previous belief that fever affected behavior. It is interesting to recognize that many parents did not predict behavior changes with fever. There are multiple possible explanations for this finding. Parents may be focused on the illness, not behaviors, during a febrile episode. Although some parents may be aware of their children's behaviors, some may not observe subtle changes. Subtle changes, if present, may not be picked up by the ABC items. Alternatively, a fever-associated behavioral response may be heterogeneous or limited to particular population subgroups. It is also not clear whether we captured the true "window" for fever-associated behavior changes. The collection of data during different time windows could have demonstrated other changes. Regarding the observed decrease in aberrant speech during fever, it is uncertain how much is attributable to illness-related features such as trouble swallowing or a decrease in spontaneous speech. Although the thermometer offers a good means to measure fever, there is a challenge in measuring illness, perhaps especially in lower functioning children who are less able to communicate about their illnesses.

Larger observational studies would facilitate comparisons among types of febrile illnesses (eg, viral versus bacterial infections, because pathogens may differentially affect behavior) as well as the addition of a comparison group of children who develop nonfebrile illnesses (eg, common cold, gastroenteritis) mentioned previously. Future studies might also include other population groups to investigate whether the phenomenon of improvement in behavior associated with fever is unique to children with ASDs. Accordingly, 1 additional group of interest would include febrile children without ASDs (eg, unaffected siblings). This would also facilitate a comparison of how well illness is measured in lower functioning children; however, a study involving these additional groups poses challenges for the recruitment of subjects and the collection of comparable data on behaviors over time. Collection of data on changes in diet, stress in the household, sleep patterns, or daily routine during febrile episodes would also be useful in future investigations.

CONCLUSIONS

This study succeeded in going beyond anecdotes and case reports in documenting behavior changes that are associated with fever in children with ASDs. More research is needed to determine with certainty whether these changes are direct biological consequences of fever and which neurobiologic pathways are involved.

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