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Do terbutaline- and mold-associated impairments of the brain and lung relate to autism?

Kaye H Kilburn, Jack D Thrasher and Nina B Immers

Abstract

Increased prevalence of the autism spectrum disorders (ASD) and the failure to find genetic explanations has pushed the hunt for environmental causes. These disorders are defined clinically but lack objective characterization. To meet this need, we measured neurobehavioral and pulmonary functions in eight ASD boys aged 8 to 19 years diagnosed clinically and compared them to 145 unaffected children from a community with no known chemical exposures. As 6 of 35 consecutive mold/mycotoxin (mold)-exposed children aged 5 to 13 years had ASD, we compared them to the 29 non-ASD mold-exposed children, and to the eight ASD boys. Comparisons were adjusted for age, height, weight, and grade attained in school. The eight ASD boys averaged 6.8 abnormalities compared to 1.0 in community control boys. The six mold-exposed ASD children averaged 12.2 abnormalities. The most frequent abnormality in both groups was balance, followed by visual field quadrants, and then prolonged blink reflex latency. Neuropsychological abnormalities were more frequent in mold-exposed than in terbutaline-exposed children and included digit symbol substitution, peg placement, fingertip number writing errors, and picture completion. Profile of mood status scores averaged 26.8 in terbutaline-exposed, 52 in mold exposed, and 26 in unexposed. The mean frequencies of 35 symptoms were 4.7 in terbutaline, 5.4 in mold/mycotoxins exposed and 1.7 in community controls.

Keywords

Autism spectral disorder, balance, blink reflex, mycotoxins, neurobehavioral tests, visual fields

Introduction

Large increases in the prevalence of autism and autism spectrum disorders (ASD) have occurred in the United States and United Kingdom. In the United States, the autism rate went from <3 to >30 per 10,000 children in the 1970s compared to the 1990s, while the prevalence in the United Kingdom increased from <10 to about 30 per 10,000 from the 1980s compared to the 1990s. Reported rates for ASD range up to 60 to 80 per 10,000 in these two countries (Baxill, 2004). Recently, the CDCP announced its ADDM study that showed a rate of 1 in 150 in 8-year-old children in multiple areas of the United States (CDCP, Mestel 2003, Carey, 2007). The causes of ASD are unknown. Proposed single gene causes are not convincing, except in Reye syndrome (Hertz-Picciotto et al., 2006; Muhle et al., 2004). Many single nucleotide polymorphisms (SNPs) including the GSTM1 null allele, GSTP1, and PON1 SNPs are associated with an increased risk of autism, most likely due to the effects they have, which result in a decreased ability to detoxify specific environmental toxins (Swanson et al 1998). On the other hand, the search for environmental chemical causes of ASD yields lead, mercury, PCBS, pesticides, and air pollution (Calderon-Garciduenas et al., 2008; Grandjean and Landrigan, 2006; Spzir, 2006a,b; Windham et al., 2006). These authors later found evidence of cognitive deficits in children from air pollution. Recent reports have connected mold exposures with neurological deficits in children and adults (Crago

Neuro-Test Inc., Pasadena, California, USA

Corresponding author:
Kaye H Kilburn, Keck School of Medicine (ret.), University of Southern California, 3250 Mesaloa Lane, Pasadena, CA 91107, USA. Email: khkilburn@sbcglobal.net

et al., 2003; Kilburn, 2003; Rea et al., 2003; Turner et al., 2007).

A new search for neurobehavioral impairment and environmental causal factors in ASD was undertaken. ASD was present in five boys whose mother had premature labor and was given terbutaline as tocolytic treatment during hospitalization. Another mother, an asthmatic, had used terbutaline aerosols (Breathine) daily during her three pregnancies. Terbutaline, a beta-adrenergic agonist and a neuro-toxicant in rats, has caused neurochemical changes leading to neuronal injury and reactive gliosis around cerebellar Purkinje cells (Owens and Sriram 1995 Rhodes et al., 2004; Zerrate et al., 2007). We postulate similar action in human subjects. Six children of 35 examined for effects of mold/mycotoxins exposure had ASD. This rate of 17% greatly exceeded the 0.7% frequency of ASD in unselected children. Mold/mycotoxins have been associated with deficiency of growth hormone and thyroid dysfunction by Dennis 2009 (this symposium). Thus, we measured neurobehavioral abnormalities of balance, reaction time, color discrimination, concentration, recall memory, multitasking, and long-term memory in these 14 ASD children, utilizing testing procedures previously reported (Crago et al., 2003; Kilburn, 2003; Rea et al., 2003).

Objectives

The objectives were to determine whether children with ASD following toxic exposures have decreased performance on standardized neurobehavioral and pulmonary tests compared to referents. The ASD children consisted of two groups: (1) mothers who either received terbutaline for its tocolytic effect while pregnant or for therapy of the mother's asthma and (2) children with ASD from moldy homes.

These are hypotheses generating observations that should help propose and develop studies that will forge connections between causes and mechanisms of ASDs particularly with observations in children.

Methods

Fourteen children, eight boys with ASD, two girls and four boys with ASD associated with mold/mycotoxin exposure had neurobehavioral measurements and completed a medical history and examination. The methods have been published repeatedly since 1982 and are reviewed briefly below (Kilburn, 2003; Kilburn and Thornton, 1995; Kilburn et al., 1998a,b). A well-standardized group of physiological tests was administered combined with psychological measures that have also been modeled statistically (Kilburn, 1998; Kilburn et al., 1998a,b). Each subject and/or parent recorded the frequency of 35 symptoms scaled 1 to 10 completed a Profile of Mood States and other feeling states inventories and questionnaires to collect historical and exposure data.

Neurophysiological tests

Simple (SRT) and two choice visual reaction time (CRT) were measured from appearance to cancellation of a 10-cm block letters, A for simple and A and S for choice (Miller et al., 1989) with a computerized instrument (Neurotest, Inc., Pasadena, CA, USA). The lowest median score of the last 7 in each of the two trials of 20 was accepted for SRT and for CRT. Body balance was measured with the subject standing erect with feet together (Kilburn and Warshaw, 1994). The position of the head was recorded (tracked) with a sound receiver from a sound-generating stylus on a headband (Neurotest, Inc.). Results were processed by a software program and expressed as mean speed of sway in cm per sec The minimal sway speed of three consecutive 20-sec trials was counted for sway with eyes open and eyes closed.

Surface electromyographic electrodes (EMG) recorded the blink reflex from the orbicularis oculi muscles (Kilburn et al., 1998a,b; Shahani and Young, 1972) after tapping right and left supraorbital notches with a light hammer, which triggered a recording computer (Neurotest, Inc.). Ten firings of R-1 were averaged for mean response for each side and failures were recorded (Kilburn et al., 1998a,b). Color discrimination as confusion index was measured with the desaturated D'Lanthony 15 hue test under 1000 Lux illumination (D'Lanthony, 1978) and scored by the method of Bowman (Bowman, 1982). Hearing in the left and right ears was measured with standard audiometers (Model ML-AM Microaudiometrics; So Daytona, FL, USA) at interval frequencies of 500 to 8,000 Hertz. The sum of deficits in both ears was the hearing (loss) score.

Neuropsychological tests

Immediate or recall memory was measured with two stories from Wechsler's Memory Scale, revised (Wechsler, 1987). Culture Fair tested non-verbal arithmetic intelligence with designs featuring similarity, difference, completion, and pattern recognition and transfer (Cattell, 1951; Cattell et al., 1941).

Culture Fair resembles Raven's progressive matrices (Raven et al., 1988). The 46-word multiple choice vocabulary test was from Jackson's multidimensional aptitude battery (Jackson, 1985). Digit symbol substitution from the Wechsler Adult Intelligence Scale-revised (WAIS-R; Reitan, 1966) tested attention and integrative capacity. Information, picture completion, and similarities also from the WAIS-R (Wechsler, 1981) tested long-term (embedded or hold) memory. Time needed to place 25 pegs in the Lafayette-slotted pegboard, and to make trails A and B were measured to assess dexterity, coordination, and decision making. Fingertip number writing measured peripheral sensation and discrimination. These were from the Halstead-Reitan battery (Reitan, 1958, 1966). Subjects' moods were appraised by responses to 65 terms describing feelings for the past week using the Profile of Mood States (POMS; *Profile of Mood States*, 1971/1981). Recall of the Rey 15 forms tested whether items recalled were appropriate or suggested malingering (Rey, 1964). Physical/neurological examinations concentrated on cranial nerves, movements, and cerebellar signs.

Respiratory flows and vital capacities were measured from a full inspiration while subjects stood and exhaled (using a nose clip) into a pneumotachygraphic spirometer (Spirovision-3 Futuremed Granada Hills, CA, USA). This maneuver was repeated until two forced expirations agreed within 5% as per ATS criteria (ATS Statement, 1987). Volume and flows measured by a computer (Spirovision-3 Futuremed Granada Hills, CA, USA). Prediction equations adjusted for height, age, sex, and smoking status (Miller et al., 1986). Alcohol was measured in air expired after a 15-sec breath hold using a fuel cell analyzer (Alcohol Intoximeter, St. Louis, MO, USA) as was carbon monoxide (Micro Smokerlyzer. Bedford TOD Instruments, England, UK).

Statistical analysis

Scores and computed data were entered into an IBM-compatible microcomputer. Descriptive and analytical computations adjusted for differences in age, education, sex, height, and weight using stepwise linear regression modeling that used Stata Statistical Software version 8 (Stata Corporation, College Station, TX, USA). These prediction equations were based on measurements of 145 school children from the neighboring state of Arizona as referents (Kilburn et al., 1998a,b). Each child's observed measurements were compared to their individual predicted values and expressed as percentage predicted. Then each observed value was compared to the predicted value based on the control group. The observed values outside the confidence intervals of the predicted values were abnormal (Kilburn et al., 1998a,b). Factors such as family income, hours of general anesthesia, POMS score, and depression score had no significant influence on the prediction equations and were excluded. Statistical significance was defined as $p < .05$. Abnormalities for each child and referents were counted after assigning bilateral tests a value of 0.5 per side, for example hearing, except visual field performance, counted 1 per side and balance with eyes open and with eyes closed were scored 1 each.

Table 1. Demographic and frequencies of findings in four groups of children

Observed	Unexposed	Mold/my	ASD/m/m	ASD terb
Number	163	29	6	8
Age years	11.7	10.6	6 (13)	13.5
Edu lev years	6.2	4.7	1.0	7.6
Sex f/m	87/76	14/15	2/4	0/8
POMS/score	26	41	52	27
SymFreq mean	1.7	3.9	5.4	4.7
ChBronc %	5	30	33	0
Chem/as %	10	80	100	25
Abn mean	0.9	2.6	12.2	6.8

ASD, autism spectrum disorders; POMS, profile of mood states. Abn mean: average number of abnormalities per child, ChBronc %: chronic bronchitis prevalence, Chem/as %: chemical hypersensitivity.

Results

Eight ASD boys aged 8 to 19 were studied and compared with control subjects after observations were adjusted for all significant factors and expressed as percentage predicted. Six ASD mold/mycotoxin (m/m)-exposed children aged 5 to 13 were similarly compared, Table 1. Values outside the confidence intervals of mean estimates were regarded and counted as abnormal.

Total abnormalities in terbutaline-exposed boys ranged from 3 to 11, with a mean of 6.8 as compared to 0.9 in controls. In the mold/mycotoxin ASD group, the mean was 12.2, with a range of 2 to 20 (2, 7, 10, 16, 16, and 20). There were only 2.6 abnormal tests in the 29 mold/mycotoxin non-ASD group. Profile of Mood States ranged from 7 to 64, with a mean of 27 in the terbutaline-exposed children, 52 in the mold/mycotoxin-exposed ASD children, 41 in the

Table 2. Abnormalities in autism spectral disorder, percentage of group

	Terbutaline	Mold/mycotoxins
Physiological tests		
Balance	88	100
Blink reflex	62	34
Visual field quad	100	(5 ND[a])
Reaction time	12	66
Psychological tests		
Digit symbol sub	50	66
Fingertip number	50	66
Peg placement	50	34
Picture completion	50	50
Pulmonary function tests	50	50

[a] ND, not done.

mold/mycotoxin without ASD group compared to 26 in unexposed children.

Frequency of symptoms on a scale of 10 had a mean of 4.7 (range 1.3 to 4.6) in the terbutaline ASD group while the mean was 5.2 and (range 3.1 to 7.2) in those mold/mycotoxin ASD exposed. In contrast, children without ASD exposed to mold/mycotoxins had mean scores of 3.9 and unexposed children had mean scores of 1.7. The specific tests are compared in the ASD groups as there were few abnormalities in those exposed to mold/mycotoxins only.

Physiological tests

Balance as speed of sway was abnormal in 88% of terbutaline boys and 100% in the mold/mycotoxin ASD children, Table 2.

Visual field quadrants were abnormal in 100% of terbutaline boys. Only one mold/mycotoxin ASD child was mature enough to do visual fields, and she was normal.

Blink reflex latency was abnormal in 63% of terbutaline and 34% mold/mycotoxin ASD children.

Reaction time was abnormal in 12% of terbutaline ASD, contrasted with while 66% with abnormal in the mold/mycotoxin ASD children. Grip strength, color differentiation errors, hearing, and vibration sensitivity were normal in both ASD groups.

Psychological tests

Digit symbol substitution was abnormal in 50% of terbutaline ASD and 66% of mold/mycotoxin ASD. Fingertip number writing errors was abnormal in 50% of terbutaline ASD and 66% of mold/mycotoxin ASD. Picture completion was abnormal in 50% of both groups. Peg placement was abnormal in 50% of terbutaline ASD and 34% of mold/mycotoxin ASD. Immediate verbal recall was abnormal in 38% and delayed verbal recall in 25%, and Culture Fair were abnormal in 25% of the terbutaline ASD boys. Only two mold/mycotoxin children could do verbal recall and Culture Fair and results were not abnormal. Vocabulary, information, and similarities were not abnormal.

Pulmonary function tests

Pulmonary function tests showed small airways obstruction in 50% of terbutaline ASD and 50% of mold/mycotoxin ASD, but no decrease in vital capacity or in forced vital capacity in 1 sec (FEV_1). One mold/mycotoxin ASD child of 13 years had asthma and a reduced FEV_1.

Discussion

ASD had been diagnosed in 6 of 35 (17%) children from families we evaluated for effects of exposure to molds and mycotoxins indoors in homes and schools from 2001 to 2007. This was 24 times the national estimated of ASD, which is 1 in 150 or 0.7% (Carey, 2007; Spzir, 2006a,b).

Terbutaline was given intravenously to the mother of five boys (same mother four different fathers) through much of the third trimester of pregnancy to reduce uterine contractions and prevent premature expulsion of the fetus, tocolytic effect. The mother of three boys had asthma and used terbutaline (Breathine) through each of her three pregnancies. The six mothers of mold/mycotoxin-exposed ASD children were not asthmatic, nor had they used terbutaline. The asthmatic mother of one subsequent ASD child who was seven years old used albuterol, a beta agonist similar in structure to terbutaline, repeatedly after the 20th week of pregnancy. He had nine abnormalities.

The two girls and four boys with mold/mycotoxin-associated ASD averaged nine abnormalities more than the terbutaline-exposed, with abnormal balance, being the most frequent. More of the mold/mycotoxin ASD children had abnormally prolonged reaction time, fewer had abnormal blink reflex latency and peg placement, but digit symbol substitution, picture completion, and fingertip number writing errors were frequent in both groups. Only one had visual field testing and it was normal. Thus these two groups appeared more similar than different. These numbers are small

so the suggested trends need to be tested with more observations.

Environmental factors are suggested to cause neurodevelopmental toxicity. They include industrial chemicals (Grandjean and Landrigan, 2006; Spzir, 2006), mercury in thimerosal (Madsen et al., 2002; Wakefield et al., 1998) and from incinerators (Palmer et al., 2006); food additives (McCann et al, 2007); measles virus (Madsen et al., 2002); agriculture pesticides (Roberts et al., 2007); testosterone (Baron-Cohen, 2003, 2005); tricyclic antidepressants; and fluoxetine (Nulman et al., 2002). Thus, mold and mycotoxin exposure should be added to the list of neurotoxic chemicals associated with ASD as well as toxic encephalopathy. Trichothecenes and aflatoxin B1 cause inflammation and neurodegeneration of the olfactory tract of rodents (Islam et al., 2006, 2007; Larsson and Tjalve, 2000). Also, occupants of mold-contaminated structure develop neurotoxicity including neurocognitive deficits (Crago et al., 2003; Kilburn, 2003; Rea et al., 2003). Finally, mycotoxins are airborne in buildings and are in the sera of exposed occupants (see Thrasher and Crawley, 2009, this symposium).

β_3-adrenoreceptors are predominant in human myometrium in pregnancy. Beta-adrenergic agonists, e.g. terbutaline, are used to control preterm labor (Rouget et al., 2005). Terbutaline readily crosses the placenta following a single intravenous (iv) dose (Bergman et al., 1984). It has been associated with ASD in dizygotic twins from tocolytic delivery (Connors et al., 2005). The administration of the drug for 2 weeks or more had an increased concordance with twins (RR = 2.0), which was increased to an RR of 4.0 for male twins. In addition, a significant association ($p < 0.006$) was found between the presence of 26G and 27E polymorphism of the beta-2-adrenergic receptors in these newborns (Connors et al., 2005).

The adverse pathology and pharmacology effects caused by terbutaline have been investigated in the neonatal rat brain at stages equivalent to specific times of human brain differentiation. Rodent studies have shown that administration of terbutaline at critical stages of neurodevelopment causes eight alterations. (1) Neuronal injury and reactive gliosis that affects the cerebellum, hippocampus, and somatosensory cortex (Rhodes et al., 2004, Sospedra and Martin 2005); (2) Robust activation of microglia results in abnormal behavior (Rhodes et al., 2004); (3) Sensitization of beta-2-adrenoreceptors to beta-agonists (Slotkin et al, 2002; Rhodes et al., 2004; Slotkin et al., 2003; Zerrate et al., 2007); (4) Oxidative stress (Slotkin et al., 2005); (5) Alterations in signaling cascades that affect cell differentiation (Cousin and Seidler, 2002; Slotkin et al., 2003, 2005); (6) Possible sensitization to the adverse effects of organophosphate insecticides (Meyer et al., 2005); (7) Probably other organ effects on heart, lens accommodation, liver lungs, etc. (Kudlacz et al., 1989; Rhodes et al., 2003; Thorkelsson and Loughead, 1992); and (8) Serotonin receptors (5HTA, 5HT2, and 5HT presynaptic transporter) were shown to have increased in expression in the midbrain, brain stem, and hippocampus after administration of terbutaline or chlorpyrifos; males were more affected than females with some regional disparities in the sex selectivity between the two agents. Both chemicals altered 5HT receptor-mediated cell signaling, suppressing stimulatory effects on adenyl cyclase and enhancing inhibitory effects. When both chemicals were administered sequentially, the outcomes were additive (Aldridge et al., 2005). Finally, neuroglia activation and neural inflammation have been demonstrated in the brain of patients with autism (Vargas et al., 2005). The neuroinflammation is characterized by increased TGF-alpha in the cerebrospinal fluid coupled with a shift toward Th2 immunity (Cohly and Panja, 2005; Chez et al., 2007) In summation, during key stages of neurodevelopment, the beta-2-adrenoreceptors are sensitized rather than desensitized. Serotonin receptors are also enhanced in numbers. These affects disrupt downstream adenyl cyclase signaling, adversely affecting neuronal cell division and differentiation. In addition, terbutaline activates microglia, leading to proinflammatory conditions and gliosis in the developing brain (Cousin and Seidler, 2001; Meyer et al., 2005; Slotkin et al., 2003; Zerrate et al., 2007). Following administration to rat pups on the second to fifth postnatal days, terbutaline caused neuronal injury shown by enzymes, glial-fibrillar acidic protein, and induction of the K-68 Dalton neurofilament protein and reactive gliosis with structural changes in cerebellum, hippocampus, and somatosensory cerebral cortex. Such effects also appear to occur in humans along with neonatal toxicity (Connors et al., 2005; Thorkelsson and Loughead, 1991).

This new hypothesis suggests that epidemiological studies that incorporate objective testing of brain and lung function and amniocentesis for chemical analysis of proteins and enzymes could yield insight into causative factors in ASD.

Summary

1. Neurobehavioral abnormalities were increased in children with ASD.
2. Several tests showed impaired brain performance in 14 ASD children. Balance was most frequently abnormal.
3. Exposures to terbutaline in-utero in eight and mold and mycotoxins at home in six were associated with abnormal neurobehavioral tests. None were exposed to both mold/mycotoxins and terbutaline.
4. Both exposures may delay development of the cerebellum and amygdala, hippocampus, and other temporal lobe structures of memory and association of the brain.

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Conflict of interest statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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