Early Markers in Infants and Toddlers for Development of ADHD

Mina Gurevitz[1], Ronny Geva[2], Maya Varon[3], and Yael Leitner[3]

Abstract

Objective: Characterization of risk factors for ADHD in infancy may enable early intervention to diminish the symptoms that ensue. **Method:** In a retrospective study, the well-baby-care clinic records from birth to 18 months of age of 58 children diagnosed at school age for ADHD were compared with those of 58 control children, and the differences between the two groups were statistically analyzed. **Results:** Eight parameters during infancy were found to be significantly associated with later development of ADHD: at 0 to 1 month—advanced maternal age, lower maternal education, family history of ADHD, and social problems; at 3 and 18 months—decrease in head circumference percentile; at 9 and 18 months—delay in motor and language development, and difficult temperament. The predictive regression model accounted for 58% of the variance. **Conclusion:** This study highlights early risk markers in infants and toddlers that may predict the development of ADHD. *(J. of Att. Dis. 2014; 18(1) 14-22)*

Introduction

ADHD, the most common neurobehavioral disorder in childhood, is characterized by attention difficulties, poor impulse control, motor hyperactivity, and restlessness (Biederman & Faraone, 2005). Worldwide epidemiological studies of ADHD have revealed a broad range of prevalence rates that depend on various factors, such as culture, ethnic origin, sex, and age. A meta-analysis of these studies pointed to an average 5.5% of children diagnosed as having ADHD (Polanczyk, Silva de Lima, Horta, Biederman, & Rohde, 2007), with a male-to-female ratio of approximately 3:1 (DuPaul, Power, Anastopoulos, & Reid, 1999). This most prevalent chronic condition frequently persists into adolescence and adulthood, and affects major aspects of life, including relationships, academic and vocational achievements, and self-esteem (Faraone, Biederman, & Mick, 2006). Children with ADHD often demonstrate deficiencies in many other cognitive abilities, for example, difficulties in physical fitness, gross and fine motor coordination, motor sequencing (Kadesjo & Gillberg, 2001), verbal and nonverbal working memory and mental computation (Barkley, 1994), and in self-regulation of emotion (Braaten & Rosen, 2000; Schachar, Tannock, & Logan, 1993). The etiological basis of ADHD is still unknown. Recent clinical overviews (Bush, 2010; Stubbe, 2000) raised two major points: (a) ADHD is heterogeneous diagnostically, developmentally, and neuropsychologically, and (b) the underlying cause for ADHD is a complex interaction between biological vulnerability and environmental triggers. The mean onset of ADHD symptoms is often perceived during preschool years, typically at ages 3 to 4 years (Connor, 2002). According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000), critical to the diagnosis of ADHD is how well the diagnostic thresholds set for the symptoms apply to age groups outside of 4 to 16 years when used in field trials (Applegate et al., 1997).

Younger preschool children aged 2 to 4 years with inattention, hyperactivity and speech, and/or motor delay, may be more vulnerable to developing ADHD at school age (Ornoy, Uriel, & Tennenbaum, 1993). However, the diagnosis of ADHD in preschool is challenging. In assessing preschool children exhibiting significant attention, or behavioral difficulties, the clinical task is to distinguish between those who may develop persistent ADHD (5%-10%) and those exhibiting transient symptoms, or ADHD-like symptoms (90%-95%; Conners, 1989). The situation with younger children (up to 2 years) is even more complex. Although restlessness, difficulties in sleeping, and

[1]Maccabi Health Services, Herzliya, Israel
[2]Bar Ilan University, Ramat Gan, Israel
[3]Tel Aviv University, Israel

Corresponding Author:
Mina Gurevitz, Maccabi Health Services, Ha'gdood Ha'ivrie Street 3/12, Ra'anana 43559, Israel.
Email: mina.gurevich@gmail.com

independent playing are regarded as "deviation from normal behavior" ("difficult temperament"), they are not considered to be an attention disorder (Greenspan & Weider, 2000). As activity level and attention in infancy are completely different when comparing toddlers or preschoolers, diagnosis of ADHD is difficult and usually would not apply to children less than 2 years old.

Evidently, early diagnosis of ADHD is a challenge because of its clinical and practical implications in enabling intervention at a period of critical changes in the rapidly developing brain to significantly diminish the severity of the symptoms and complications that may develop.

Materials and Method

General Information

All babies in Israel are routinely followed in well-baby-care clinics from birth till 5 years of age under the supervision of the Ministry of Health, and thus their health profiles are documented. Children insured by Maccabi Health Services in the town of Herzliya who are suspected for behavioral and attention difficulties are being referred to an ADHD center. As a pediatrician of the baby-care clinic of Maccabi Health Services in Herzliya, Mina Gurevitz meticulously examined, documented, and followed a large number of babies (averaging 2,500 per year), and had access to their files at Maccabi database.

Participants

58 children diagnosed for ADHD in accordance with the DSM-IV criteria were selected in 2008 for this study. The detailed charts of these children were available to MG, who followed them during early childhood at the well baby-care clinic. A control group comprising 58 children was randomly selected from the same well-baby-care database to match gender and birth date of the ADHD group. The charts of the control children were reviewed to exclude ADHD symptoms or diagnosis, or the usage of ADHD medications. Their corresponding well-baby-care charts at identical time points during follow-up were reviewed and compared with those of the ADHD group. Premature infants, babies with chronic illnesses, or those diagnosed at a later stage as having any major developmental disorder were excluded from the study. This study was approved by the Maccabi Health Insurance Services Research Committee, and no patient consent was required.

Covariates

The following pertinent data were collected from the charts containing in detail evaluations of the babies during the 0 to 1, 3, 9, and 18 months visits to the well-baby-care clinic:

1. *Family history:* Parental age and occupation, family size, birth order, and ADHD in siblings. Social problems, such as divorce, socioeconomic difficulties, and parental illness (mental or physical) were also recorded.

2. *Perinatal and postnatal history:* Length and progress of pregnancy, type of delivery, infant's birth weight, and Apgar scores.

3. *Biometric parameters of the infant/toddler:* Weight, height, and head circumference (HC) percentiles.

4. *Infant/toddler nutrition:* Breast or bottle feeding (extracted breast milk or formula) in accordance with "The Israeli guidelines for infant nutrition" (Ministry of Health Israel, 2009).

5. *Developmental milestone achievement rates:* Gross and fine motor, language and speech, and cognitive and communication evaluations following the Denver Developmental Screening Test (DDST; Frankenburg & Dodds, 1967).

6. *Commonly encountered difficulties during the first 3 months:* Infant colic and gastroesophageal reflux (Reust & Blake, 2000; Roberts, Ostapchuk, & O'Brien, 2004; Rudolph et al., 2001) were clinically inferred by the pediatrician based on the parental description of outbursts of strong cries and recurrent, multiple episodes of spitting-up and/or vomiting.

7. *Sleep and feeding problems:* Sleep problems were recorded as the difficulty to fall asleep independently, recurrent awakening during the night accompanied by struggle in resuming sleep, and very short naps during the day (White, Gunnar, Larson, Donzella, & Barr, 2000). Feeding problems were defined as difficulties in switching from breast feeding to bottle feeding and from breast milk to formula. This also included difficulties on transition to spoon feeding of solid food, maintaining a daily routine by regulating food amounts, and maintaining constant intervals between feedings (Slining, Adair, Davis Goldman, Borja, & Bentley, 2009).

8. *Child temperament as described by the parents and observed by the pediatrician during the visit:* Three types of temperaments were recognized. The "difficult child" was defined as restless, irritable, easily frustrated, and nervous, with difficulties in postponing immediate satisfaction. The "slow to warm-up child" was characterized as being quiet, calm, sleepy, and slow reacting. The "easy child" was considered "normative" and served as control (McDevitt & Carey, 1978).

9. *Behavior characteristics:* These characteristics were classified by the degree of cooperation during doctor visits. A cooperative infant was

usually calm, quiet, and easily consoled during physical examinations, while the uncooperative child tended to cry constantly and could hardly calm down. Recording of the usage of a transfer object (towel or napkin), a pacifier, or thumb sucking was documented, as was a refusal to accept a pacifier or a bottle. At the 9-month visit, information regarding the sensory profile and degree of dependency (separation and stranger anxiety) was added. At the 18-month visit, data concerning social behavior, such as shyness, insecurity, and frustration threshold were included.

10. *Abnormal findings on physical examination:* The general tone, head and neck control, hyperlaxity of ligaments, or any physical or neurological abnormality were recorded.

Statistical Analysis

To compare the biometric measures with the social and developmental outcome parameters of the children, unpaired *t* test was used for parametric measures. The Wilcoxon's nonparametric test and the Pearson chi-square analyses were performed to compare differential frequencies. In addition, adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. The logistic regression model was used to examine the predictive added power of the dependent parameters at each age to predict later diagnosis of ADHD.

Results

Participant demographic characteristics are shown in Table 1. The ADHD group comprised 58 children (69.0% boys and 31.0% girls), mean age 8.17 ± 1.43 years at the time of diagnosis of ADHD. The control group was matched in number of children gender (65.5% boys and 34.5% girls, *p* = .422), and age (7.77 ± 1.31 years, *p* = .123).

Family Background

The study was conducted in a suburban area in the center of Israel using a population sample from a high-average socioeconomic status. All fathers and 85% of the mothers of the children in the ADHD and control groups were employed. In the ADHD and control groups, mean maternal ages were 32.93 ± 6.04 and 30.94 ± 3.55 years (*p* = .040), respectively, and paternal ages were 36.72 ± 6.72 and 34.20 ± 5.06 years (*p* = .028), respectively (Table 1). Most children in the ADHD group were raised in families with a relatively lower parental academic education according to their parents' profession: 25.9% of the mothers and 26.9% of the fathers of ADHD children had an academic profession compared with

54.5% of the parents of children in the control group (*p* = .002). In the ADHD group, 15.5% of the children had a sibling diagnosed with ADHD compared with 0.0% for the control group (*p* = .001). Significant social problems, such as divorce or chronic illness, were reported in 15.5% and 1.7% of families in the ADHD and control groups, respectively (*p* = .008).

Perinatal History

Pregnancy was uneventful and full term in both groups (*p* = .455). The number of normal vaginal deliveries (63.8%) and planned cesarean sections (14.6%) was identical in both groups. Whereas vacuum delivery was more frequently performed in the control group (15.5% vs. 3.4%, *p* = .027), the number of emergency cesarean sections was significantly higher in the ADHD group (12.1% vs. 0%, *p* = .001). Apgar score of 90% of the children in both groups was 9 at 1 min, and no difference was found in average birth weight (Table 1).

Biometric Parameters

A significant difference was found between HC percentile in the ADHD and control groups (Table 2). The HC percentile was smaller at 3 months of age in the ADHD group (*p* = .002) and much smaller at 9 and 18 months of age (*p* = .001) in contrast to the controls. This difference clearly reflected on the decrease in HC growth rate (at 3 months OR = 1.026, 95% CI = [1.045, 1.008], *p* = .005; at 9 months OR = 1.029, 95% CI = [1.048, 1.011], *p* = .001; at 18 months OR = 1.031, 95% CI = [1.052, 1.011], *p* = .003). No difference was observed in weight and height percentiles between the groups. As shown in Figure 1, the average HC percentile of children later diagnosed for ADHD decreased significantly since birth compared with those in the control group. From 3 to 9 months of age, the difference between the groups increased (from *p* = .002 to *p* = .001) and then persisted until 18 months of age (*p* = .001). The HC demonstrates a decrease in percentile in 61% of the children in the ADHD group, and only 24.6% followed a constant HC growth curve. In comparison, 79.3% of the control infants followed a constant HC percentile curve. The average HC-to-length ratio was 0.74 ± 0.04 in the ADHD group and 1.09 ± 0.05 (*p* = .06) in the control group.

Developmental Milestones and Physical Findings

Children with ADHD exhibited a significant delay in motor development compared with children of the control group (Table 3). At 3 months of age, 44.8% of the ADHD infants had gross motor developmental delay compared with 19.0% of the controls (*p* = .002). The difference between the ADHD and control groups was reflected clearly in the

Table 1. Demographic Characteristics.

Parameter	ADHD/ADD (n = 58)	Controls (n = 58)	*p*
Gender (male/female)	40/18 (69.0%/31.0%)	38/20 (65.5%/34.5%)	.422
Current age (years)	8.17 ± 1.43	7.77 ± 1.31	.123
Gestational age (weeks)	39.44 ± 1.41	39.61 ± 1.05	.455
Birth weight (kg)	3.36 ± 0.42	3.32 ± 0.98	.645
HC (cm; mean at 0-1 month)	48.3 ± 28.9	57.6 ± 25.5	.075
Apgar at 1 min	8.75 ± 0.95	8.98 ± 0.30	.089
Apgar at 5 min	9.93 ± 0.26	9.95 ± 0.23	.717
Maternal age (years)	32.93 ± 6.04	30.94 ± 3.55	.040
Paternal age (years)	36.72 ± 6.72	34.20 ± 5.06	.028
Maternal academic occupation	25.9%	54.5%	.002
Paternal academic occupation	26.9%	54.5%	.003
Family history of ADHD	15.5%	0.0%	.001
Family social problems	15.5%	1.7%	.008

Note: ADD = attention deficit disorder; HC = head circumference.

Table 2. Biometric Parameters in Percentiles at 3, 9, and 18 Months of Age.

Age (months)	HC (ADHD, n = 58)	HC (controls, n = 58)	*p*	Weight (ADHD, n = 58)	Weight (controls, n = 58)	*p*	Height (ADHD, n = 58)	Height (controls, n = 58)	*p*
3	51.4 ± 24.8	64.5 ± 19.1	.002	69.2 ± 21.5	70.1 ± 16.4	.795	60.5 ± 22.6	61.2 ± 20.0	.847
9	40.2 ± 29.3	56.5 ± 20.3	.001	51.8 ± 25.9	58.5 ± 22.4	.137	59.7 ± 24.8	58.7 ± 24.2	.825
18	37.4 ± 30.3	54.9 ± 21.5	.001	56.4 ± 26.9	61.2 ± 22.4	.300	61.7 ± 24.4	57.9 ± 26.5	.419

Note: HC = head circumference.

motor developmental delay (at 3 months of age OR = 0.31, 95% CI = [0.743, 0.129], *p* = .009). At 9 and 18 months of age, gross motor developmental delay was observed in 34.5% and 13.8% (*p* = .008), and 12.1% and 1.7% (*p* = .030) of the ADHD and control groups, respectively (at 9 months of age OR = 0.254, 95% CI = [0.755, 0.085], *p* = .014; at 18 months of age OR = 0.043, 95% CI = [0.438, 0.004], *p* = .008). At 9 and 18 months of age, the ADHD group had a significant delay in speech and language development (*p* = .001; at 18 months of age OR = 0.037, 95% CI = [0.124, 0.011], *p* = .0001). At 18 months of age, 20.7% of the toddlers, later diagnosed for ADHD, were uncooperative during doctor visits at the well-baby-care clinics in comparison with 5.2% of the toddlers in the control group (*p* = .012). Abnormal physical findings were observed in the ADHD group at the 3-month visit: 21% had hypotonia and lax ligaments, 7% were hypertonic, and 7% had deformational plagiocephaly. None exhibited other neurological abnormalities.

Feeding, Sleeping, and Self-Regulation

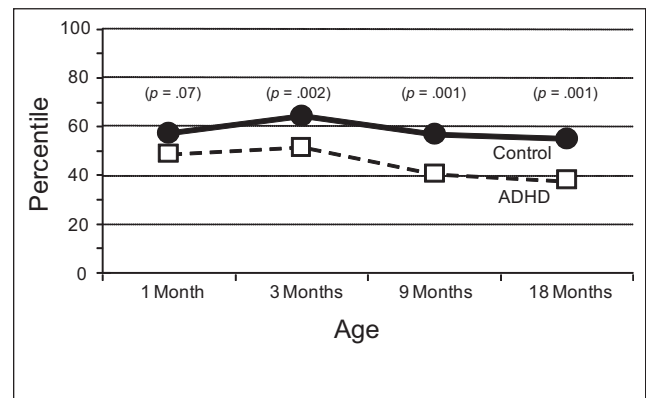As shown in Table 4, at 3 months of age, infants in the ADHD group suffered more frequently from infant colic

Figure 1. Average of head circumference percentile measurements at birth to 1, 3, 9, and 18 months in ADHD and control groups.

(17.2% vs. 8.6%, respectively, *p* = .236) and gastroesophageal reflux (22.4% vs. 10.3%, respectively, *p* = .200) than the control group, although this did not reach statistical significance. The gastroesophageal reflux symptoms persisted throughout the entire 1st year in the infants later diagnosed for ADHD (32.7% vs. 12.0%, *p* = .018). These infants experi-

Table 3. Developmental Milestone Achievement Rates and Child Behavior During the "Well-Baby-Care" Visit at 3, 9, and 18 Months of Age.

	9 months			18 months		
	ADHD (n = 58)	Controls (n = 58)		ADHD (n = 58)	Controls (n = 58)	
Parameter	% of children		p	% of children		p
Uncooperative behavior	3.4	1.7	.500	20.7	5.2	.012
Delay in language/speech	31.0	1.7	.001	63.8	8.6	.001
Delay in gross motor development[a]	34.5	13.8	.008	12.1	1.7	.030
Delay in fine motor development	5.2	0.0	.122	8.6	3.4	.219

[a]At 3 months: p = .002 (44.8% ADHD/19.0% controls).

Table 4. Commonly Encountered Difficulties During the First 3, 9, and 18 Months of Age.

	3 months			9 months			18 months		
	ADHD (n = 58)	Controls (n = 58)		ADHD (n = 58)	Controls (n = 58)		ADHD (n = 58)	Controls (n = 58)	
Parameter	% of children		p	% of children		p	% of children		p
Infant colic (% of babies)	17.2	8.6	.236						
Gastroesophageal reflux (% of babies)	22.4	10.3	.200	10.3	1.7	.133			
Sleep difficulties	12.1	0.0	.006	29.3	32.8	.421	29.3	24.1	.338
Feeding problems	17.2	1.7	.004	24.1	10.3	.042	13.8	6.9	.181

enced significantly more difficulties in regulation of sleep (12.1% vs. 0.0%, *p* = .006) and feeding (17.2% vs. 1.7%, *p* = .004; Table 4) as documented at the 3-month visit. They had more feeding problems than control infants as documented at the 9-month visit (24.1% vs. 10.3%, *p* = .042).

Behavioral Characteristics

A comparison was made between the groups regarding their behavior characteristics as described by their parents and noted by the pediatrician during the well-baby-care visits. A chi-square nonparametric test of the frequency of behavior-characteristic–related risks is summarized in Table 5, indicating that the number of "easy" children with a normative temperament in the ADHD group was significantly lower (62.1%) than that in the control group (89.7%) at 9 months of age (*p* = .002; OR = 0.177, 95% CI = [0.495, 0.063], *p* = .001), and 46.6% versus 81.0%, respectively, at 18 months of age (*p* = .001; OR = 0.319, 95% CI = [0.667, 0.153], *p* = .002). Although some of the observations might appear subjective in the eyes of the pediatrician, notably, the data collection was unbiased as the initial well-baby-care records were documented before any diagnosis was known or suspected.

Multivariate Regression Model

Serial regression analyses were conducted to trace the best predictor for ADHD at each age of the well-baby-care follow-up. Final analysis was then performed with the background parameters entered in the first step, followed by the best clinical predictors, entering younger ages in earlier steps and those from older ages in the final steps of the regression. Demographic data, such as maternal education and age, social problems in the family, and a sibling with ADHD were found to account for 25% of the variance described. A decrease in HC percentile and sleep problems found at 3 months of age accounted for 14.2% of the variance. At 9 months of age, motor developmental delay, difficult behavior, and language delay accounted for 27.9% of the variance described. Decrease in HC percentile, difficult behavior, speech delay, and feeding problems accounted for 44.2% of the variance. The overall predictive model accounted for 58% of the variance explained: Background factors (maternal age, maternal education, and presence of siblings with ADHD in the family) accounted for 21.8%. The best predictor from 3 months of age, the smaller HC percentile, added an additional 5% to the variance. Finally, an additional 27% were related to best predictors from 18

Table 5. Behavioral Characteristics.

	Easy child			Difficult child			Slow to warm-up child		
Age	ADHD/ADD (%)	Controls (%)	*p*	ADHD/ADD (%)	Controls (%)	*p*	ADHD/ADD (%)	Controls (%)	*p*
9 months	62.1	89.7	.002	32.8	10.3	.003	5.2	0.0	.122
18 months	46.6	81.0	.001	41.4	17.2	.004	12.1	1.7	.030

Note: ADD = attention deficit disorder.

months of age (i.e., persistent smaller HC percentile at 18 months of age, difficult temperament and delayed speech, and language development).

Discussion

ADHD is an extremely prevalent disorder usually diagnosed at school age. This syndrome places a significant burden on the medical establishment in providing diagnosis and treatment. Yet, despite the evident need, studies aiming at the identification of clinical risk factors in infancy and preschool age are scarce (Auerbach, Atzaba-Poria, Berger, & Landau, 2004; Hartsough & Lambert, 1985; Ilott, Saudino, & Asherson, 2010; McMenamy, Sheldrick, & Perin, 2011; Szatmari, Offord, & Boyle, 1989). Our retrospective study delineates early clinical markers predictive for the development of ADHD. These markers are advanced maternal age and lower education of the mother; ADHD in a sibling; social problems in the core family; decrease in HC percentile with regression from initial trajectory; delay in motor, speech and language development; and behavioral problems reflected by difficult temperament. The possible genetic etiology of ADHD development as well as the social problems in the core family (e.g., stress, marital conflicts, separation and divorce, maternal depression) are in agreement with previous reports (Barkley, 2006; Szatmari et al., 1989). However, our findings about maternal age and socioeconomic status contradict previous studies that linked the development of ADHD with younger age of mothers and the low socioeconomic status of the families (Cunningham, Benness, & Siegel, 1988; Lambert, Sandoval, & Sassone, 1978; Linnet et al., 2003; McIntosh, Olshan, & Baird, 1995; Pineda et al., 1999; Szatmari, 1992). We reasoned that this difference might be associated with the preference of women at the upper-middle socioeconomic class at the Herzliya region to give birth at a later stage in life.

A salient difference between the two study groups was the decrease in head growth rates of individuals later diagnosed for ADHD. Whereas the HC growth rate in the control children was almost constant from birth to 18 months of age, the head growth rate of children in the ADHD group slowed down during that period (Figure 1). This is conceivable taken that ADHD is associated with a smaller total brain volume (Krain & Castellanos, 2006). Recent studies using quantitative magnetic resonance imaging (MRI)

have indicated significantly smaller anterior right frontal regions, smaller size of the caudate nucleus, and smaller globus pallidus regions in children with ADHD compared with control participants (Aylward et al., 1996; Castellanos et al., 1996; Filipek et al., 1997; Pauls, 1991). Smaller HC and a smaller HC-to-length ratio in full-term infants with intrauterine growth retardation have also been correlated with behavioral symptoms of ADHD (Kelly, Nazroo, McMunn, Boreham, & Marmot, 2001; Lahti et al., 2006). Our hypothesis is that absolute HC values, particularly of small size, are insufficient for prediction of developmental deviations, yet dysregularities in HC growth are an early predictive marker for developmental problems, such as ADHD. To the best of our knowledge, this study is the first to suggest a correlation between decrease in head growth percentile during early infancy and development of ADHD at a later stage in life.

At 9 months of age, the three major parameters predictive of later development of ADHD are delays in motor development, delays in speech and language, and behavioral difficulties. Developmental delays have already been reported in association with the development of ADHD (Auerbach et al., 2004; Barkley, DuPaul, & McMurray, 1990). In our study, the delay in motor development was relatively mild and could be attributed in part to physical characteristics, such as hypotonia and lax ligaments. Although most children of the ADHD group developed within the acceptable wide range of the motor milestone achievement rate, they performed at the "extremes," being either early or late achievers. They often refused to stay in a prone position and preferred the supine position, which led to difficulties in head control and further to a motor developmental delay. Our results are in agreement with reports on "soft" neurological signs related to developmental coordination disorder and motor overflow movements that are more common in children with ADHD (Carte, Nigg, & Hinshaw, 1996).

According to our study, a delay in speech and language is the most significant factor for predicting the development of ADHD at 9 and 18 months of age. One third of the infants of the ADHD group experienced a delay in speech development at 9 months of age, and two thirds experienced a delay in speech and language development at 18 months of age. This is consistent with other studies of children with ADHD (Humphries, Koltun, Malone, & Roberts,

1994). Temperamental and behavioral problems at 9 and 18 months of age are an additional important predictive factor for the development of ADHD. It has been previously described that excessive crying during infancy was followed by later problems in sensory integration, attention, and behavioral development (DeSantis, Coster, Bigsby, & Lester, 2004). Thus, the main markers at 18 months of age that correlated with later development of ADHD are decreasing HC percentile, difficult behavior characteristics, and speech and language developmental delay.

In summary, we took advantage of the Israeli well-baby-care infrastructure and detailed clinical records to collect data regarding the early infancy of children later diagnosed for ADHD. Despite the limitations of a retrospective study, the meticulous documentation of clinical data and careful observations enabled the analysis performed in this study that unraveled early markers predictive for the development of ADHD. These markers create a "clinical profile" that can be used by the clinician to predict ADHD development, thereby enabling early intervention, such as parental guidance, in an effort to diminish the expected future complications. In light of the new guidelines by the American Academy of Pediatrics Subcommittee on ADHD, Committee on Quality Improvement, 2011, such early markers may further aid in the diagnosis of preschool ADHD.

Conclusion

This study provides novel early markers that may predict the development of ADHD, which has shown tremendous increase in recent years. As early intervention might diminish the complications that entail ADHD, a detailed clinical screening system using the proposed early markers to pinpoint individuals with risk of developing ADHD might be highly beneficial to the public as well as to the medical system. The present study reveals that up to the age of 18 months, the development of ADHD might be predicted in as much as 58% of the patients on careful follow-up of parameters, such as HC percentile, delay in milestone achievement rates, extreme temperament, and familial background.

Authors' Note

Declaration of Conflicting Interests

Funding

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Author Biographies

Mina Gurevitz, MD, is a primary care pediatrician, Board certified in USA and ISRAEL, with subspecialty in pediatric gastroenterology and child development (early infancy). Her research focus is on early detection and intervention of neurobehavioral problems in children.

Ronny Geva, PhD, has been a Fulbright scholar during her PhD studies at the City University of New York. She has been chair of the Clinical Child and Adolescence Psychology and the head of the Developmental Neuropsychology laboratory at the Gonda Brain Research Center program at Bar Ilan University. Dr. Geva is author of multiple peer-reviewed papers and book chapters on self regulation and attention deficits of infants at-risk.

Maya Varon, Msc, is a statistician graduated at the Tel Aviv University, Faculty of Business Management.

Yael Leitner, MD, is a senior Pediatric Neurologist and the director of the Tel- Aviv Child Development Center and pediatric ADHD clinic, affiliated with the Sackler School of Medicine at Tel-Aviv University. She is a senior lecturer in pediatrics, the organizer of the continuous medical education course in developmental neurology and the secretary of the Israeli Child Development Society. Her research interests center around risk factors in Developmental Disabilities, prematurity, Intrauterine Growth Retardation and the later impact of minor fetal MRI abnormalities on neurocognitive development.