Screening for autism in low-birth-weight Egyptian toddlers

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Background

In recent times major advances have been made in the field of early detection of autism in infants, and validated screening tools now exist to facilitate the early and accurate screening of infants before further referral for specialized autism diagnostic testing.

Objective

The aim of this study was to screen low-birth-weight (LBW) toddlers for early autistic features compared with normal controls and identify the associated risk factors.

Materials and methods

This cross-sectional study included 100 toddlers (24–30 months old) with a history of LBW. They were screened for autism using the Modified Checklist for Autism in Toddlers (M-CHAT). Further assessment was made using the Childhood Autism Rating Scale (CARS), Vineland Social Maturity Scale, and Arabic Language Test. One hundred age-matched and sex-matched full-term toddlers with a history of average birth weight and uneventful natal, perinatal, and postnatal history were included as the control group.

Results

The toddlers with LBW had a significantly higher frequency of positive M-CHAT screening than did the controls (11% of LBW children vs. 2% of controls). Positively screened LBW toddlers had significantly higher parental age at conception, lower birth weight, higher frequency of small-for-gestational-age preterms as well as higher incidence of gestational bleeding when compared with negatively screened LBW. They also had lower language and social ages than the negatively screened LBW. M-CHAT scores of positively screened LBW children correlated positively with maternal age at conception and negatively with birth weight, social age, and language age. Five of the 11 positively screened LBW children and one of the two positively screened controls were confirmed to have autism on the basis of CARS.

Conclusion

LBW is probably an independent risk factor associated with the development of autism. Early screening for autism is recommended for the LBW population especially if associated with risk factor(s) or if showing early impairment of social and language abilities, to be followed by definitive autism testing in those with positive screening results.

Introduction

Autism is a neurodevelopmental disorder characterized by deficits in social interaction and communication, both verbal and nonverbal, together with restricted, repetitive interests and behaviors with an onset before 3 years of age [1–3]. It was previously reported to have a median rate in epidemiological studies of five cases per 10 000 individuals, with reported rates ranging from 2 to 20 cases per 10 000 individuals [3]. Its incidence has risen 10-fold since the early 1980s, with most of this increase not explainable by changing diagnostic criteria [4]. Recently, the prevalence of autism spectrum disorders (ASDs) in the USA was estimated to be one in 110 individuals [5].

It is now believed that the mechanism underlying autism etiology is most likely an interaction of environmental and genetic factors [6,7]. Although the distinctive neuropathology remains elusive, studies have shown macroscopic, microscopic, and functional brain abnormalities, [6–8] which suggest that the etiologically relevant period may be *in utero* because the pathogenesis may begin during the prenatal period [6].

Pregnancy-related exposures have been the focus of a significant amount of epidemiological research on possible risk factors for autism [9]. It was stated by Kolevzon *et al.* [10] that many studies support the hypothesis that obstetrical complications, especially those inducing

intrapartum hypoxia, as well as prenatal or intrapartum use of medications [11,12] may possibly increase the risk of autism.

Despite significant research into the potential role of pregnancy and birth complications in the origin of autism, the causal nature of these associations is still disputed [10]. Low birth weight (LBW) is caused by preterm birth, intrauterine growth retardation, or by both [13]. Prematurity and LBW have been considered important risk factors of abnormal cognitive development during early childhood [14,15] as well as for disturbances in social interaction, communication, and behavior [16]. The incidence of LBW delivery is variable in developed and developing countries. For instance, it is estimated to be 12% in Egypt [14], whereas it is only 3% in Norway [17].

Validated screening tools now exist to facilitate the early and accurate screening of infants and to identify clinical predictors of positive autism screening results before further referral for specialized autism diagnostic testing [18,19]. The Modified Checklist for Autism in Toddlers (M-CHAT), consisting of 23 yes/no items, including six items pertaining to social relatedness and communication is used as a reliable instrument for the early detection of autism [20].

To achieve an earlier detection of and intervention for autism, being the core of the ASDs, we decided to screen for early autistic features in a cohort of LBW toddlers compared with a normal control group. The objective of this study was screening for early autistic features in LBW toddlers in comparison with normal average-birth-weight full-term toddlers and identification of risk factors associated with positive screening for autism in this population.

Subjects and methods
Subjects
The current cross-sectional study was conducted on 100 Egyptian LBW toddlers with birth weight less than 2500 g who were either full-term small for gestational age (SGA) or preterm small, appropriate, or large for gestational age, according to Smith [21]. We excluded very-low-birth-weight toddlers – that is, children less than 1500 g. The children were selected from the neonatology clinic, then followed up at pediatric outpatient clinics, and further assessed at the Phoniatrics Clinic of Ain Shams University hospitals during the period from January 2009 to October 2011. Toddlers with audiological disorders, abnormal gross neurological deficits, grossly delayed motor or mental development, positive family history of autism, or with a known chromosomal disorder were also excluded. The studied toddlers comprised 58 (58%) boys and 42 (42%) girls. Their mean age was 26.5 ± 1.99 months (range 24–30 months). Age-matched and sex-matched 100 normal Egyptian children with a history of full-term delivery, average birth weight, and uneventful prenatal, natal, and postnatal history were included as the

control group. They were selected from pediatric outpatient clinics, Ain Shams University hospitals, during the same period. They comprised 54 (54%) boys and 46 (46%) girls. Their mean age was 26.7 ± 2.2 months (range 24–30 months).

Methods
All the LBW children were subjected to the following examinations.

Parents' interview and examination
This included full history taking, giving special consideration to maternal and paternal ages at conception, prenatal, natal, and postnatal history, milestones of motor and language development, history of hearing troubles, head trauma or fits, and subjective impression of sociability, surrounding environmental factors, and parental care.

Subjective language evaluation was done to assess the child's inner language, passive vocabulary (ability to recognize different semantic groups), and active vocabulary (how many single words could the child utter and the length of the sentence). Audiological assessment and neurological and vocal tract examinations were performed to exclude cases with any disorders. Further assessment of language abilities was done for each child of the LBW group using the Arabic Language Test according to Kotby *et al.* [22].

The modified checklist for autism in toddlers: Robins et al. [20]
The M-CHAT is an extension of the Checklist for Autism in Toddlers (CHAT), proposed by Baron-Cohen *et al.* [23]. The M-CHAT is a 23-item (yes/no) parent-report checklist [20]. It includes items for assessment of certain functions or their precursors: for example, sensory abnormalities (undersensitive or over-reaction to noise), motor abnormalities (unusual finger movements, climbing), social interchange (eye contact, smiling in response to parent's smile), early joint attention/theory of mind (bringing objects to show parents, pointing to indicate interest, following an adult's words), and early language and communication skills (pointing to request, indicating own wishes, responding to name) [20]. Psychometric data from the M-CHAT demonstrate high sensitivity and specificity [24]. An Arabic double-translated handout checklist form of M-CHAT was prepared and explained to parents and were answered by them. The cutoff criteria by which the child fails the M-CHAT and is therefore considered to have a positive M-CHAT screening result was set to failure of two of the critical items or of any three items [20].

Childhood Autism Rating Scale: Schopler et al. [25]
It is widely recognized and used as a reliable instrument for the diagnosis of autism [26]. It is a 15-item structured interview and observation instrument. The examiner assigns a score of 1–4 for each item: 1 indicates behavior appropriate for age level, whereas 4 indicates severe deviance with respect to normal behavior for age level. Each item is rated on a 4-point scale, which may be

extended to 7 points by insertion of intermediate points as the child may be rated between two descriptions by using ratings of 1.5, 2.5, or 3.5. The total score of the test can range from 15 to 60 points according to the severity of autism. The score can be categorized into: nonautistic (<30), mild to moderately autistic (30–36.5), and severely autistic (>36.5) [27].

Social age determination

Social age was determined by the Vineland Social Maturity Scale of Doll [28]. This scale is applied to assess the social behavior and abilities of children and is suitable for children from birth to 15 years. It is a discriminative norm-referenced measure of functional status in a wide range of adaptive skills, including communication (receptive, expressive, and written), daily living (self-help in dressing and eating), socialization (interpersonal relationships, play and leisure time, and coping skills), motor (gross and fine skills), self-direction, and occupation.

Control group: All the participants of the control group underwent the M-CHAT screening, whereas Childhood Autism Rating Scale (CARS) assessment was done only for children screened positively for autism.

Statistical analysis

The data were coded and entered using statistical package SPSS, version 12 (SPSS Inc., Chicago, Illinois, USA) for Windows and summarized using mean ± SD for quantitative variables and number and percentage for qualitative data. Student's *t*-test was used to compare quantitative variables. The χ^2-test was used to compare qualitative data. Correlation matrix for two variables was done using Pearson's correlation (r) to assess the association between the different parametric data. *P* values less than 0.05 were considered significant.

Results

Low-birth-weight group

The LBW group comprised 67 (67%) preterm and 33 (33%) term children of a mean gestational age of 36.2 ± 2.5 weeks (range 32–41 weeks) and mean birth weight of 2004.5 ± 278.8 g (range 1550–2450 g). Among the preterm children, 59 (88%) were appropriate for gestational age (AGA); birth weight was greater than or equal to the 10th percentile for gestational age, and eight children (12%) were SGA; birth weight was lower than the 10th percentile for gestational age. All the full-term children were SGA.

Eleven (11%) of the LBW children had positive M-CHAT screening results with M-CHAT scores ranging from 2 to 12. Five of them (45.5%) were diagnosed with autism using CARS (three children with mild-to-moderate autism and two children with severe autism) with a mean score of 35 ± 3.9 points (range 30–39). All the remaining negatively screened LBW children ($n = 89$) were considered nonautistic as they had CARS scores less than 30.

Control group

Two (2%) children in the control group had positive results on the M-CHAT, and only one of them (50%) had a positive result on the CARS assessment, which revealed mild-to-moderate autism (score = 32).

An overall 13 children in both groups showed positive M-CHAT (11 children in the LBW group and two in the control group). Of them, three LBW children (23.1%) were positive on the basis of failure of two critical items only. Two children (15.4%) failed one critical item and two others failed noncritical items (one LBW child and one control). Meanwhile, five children (38.4%) failed two critical items in addition to other four to eight noncritical items (five LBW children). The remaining three children (23.1%) with positive screening failed at least three critical items in addition to other six to nine noncritical items (two LBW children and one control).

On comparison, there was significantly higher frequency of positive M-CHAT screening in the LBW group than in the control group ($P<0.05$), as shown in Fig. 1.

The LBW group was further subdivided according to the M-CHAT screening results into two subgroups: the positively screened LBW subgroup ($n = 11$) comprising seven (63.6%) boys and four (36.4%) girls and the negatively screened LBW subgroup ($n = 89$) comprising 51 (57.3%) boys and 38 (42.7%) girls.

No significant difference was detected between the two subgroups with regard to gender and gestational or chronological ages. The positively screened LBW subgroup showed highly significant ($P<0.001$) LBW and higher maternal and paternal age at conception, as well as significantly ($P<0.05$) higher frequency of SGA preterms compared with the negatively screened subgroup (Tables 1 and 2). Meanwhile, there were no significant differences ($P>0.05$) in frequencies of SGA full-terms and AGA preterms on comparing the two

Figure 1
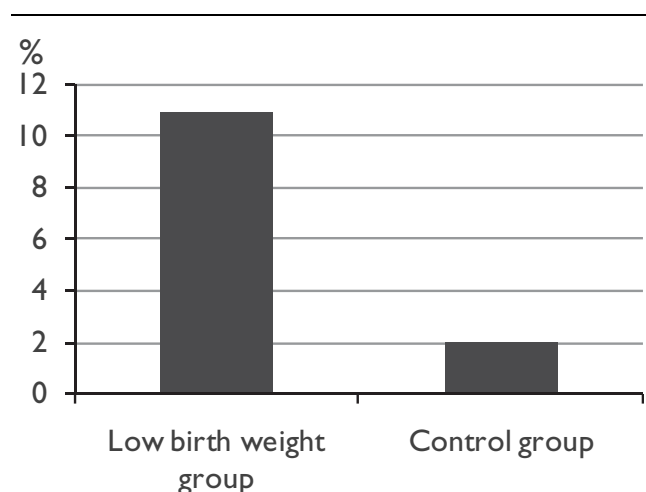
Comparison between the low-birth-weight group and the control group with respect to the frequency of positive M-CHAT screening. M-CHAT, Modified Checklist for Autism in Toddlers.

Table 1 Comparison between the two low-birth-weight subgroups with respect to the different demographic and clinical data

Variables	Positively screened LBW (mean ± SD)	Negatively screened LBW (mean ± SD)	Significance
Chronological age (months)	25.8 ± 1.5	26.6 ± 2.2	$P > 0.05$
Maternal age at conception (years)	35.2 ± 4.8	29.3 ± 4.6	$P < 0.001$**
Paternal age at conception (years)	42.5 ± 4.5	35.5 ± 4.8	$P < 0.001$**
Gestational age (weeks)	35.5 ± 2.6	36.1 ± 2.3	$P > 0.05$
Birth weight (g)	1727.3 ± 160.3	2056.3 ± 263.7	$P < 0.001$**
Language age (months)	14 ± 4.4	23.9 ± 4.6	$P < 0.001$**
Social age (months)	14.6 ± 1.9	26.2 ± 3.2	$P < 0.001$**

LBW, Low birth weight.
**Highly significant.

Figure 2
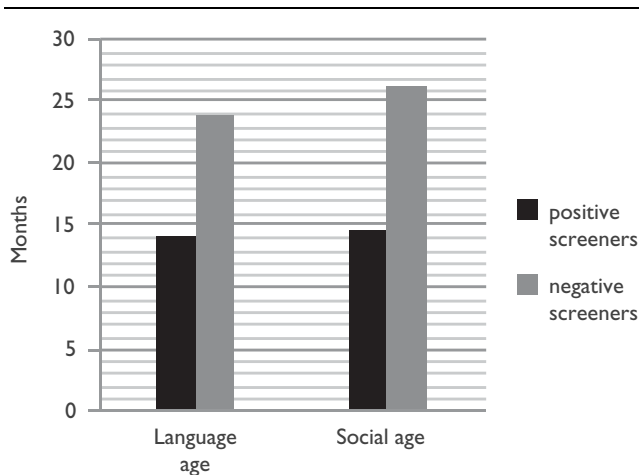
Comparison between low-birth-weight toddlers with positive M-CHAT screening and low-birth-weight toddlers with negative M-CHAT screening with respect to language and social abilities. M-CHAT, Modified Checklist for Autism in Toddlers.

subgroups. Nine (81.8%) children among positively screened LBW children and six (6.7%) among negatively screened LBW children showed delayed language development with highly significant ($P < 0.001$) lower language and social ages in the former than in the latter (Table 1 and Fig. 2).

Having one or more risk factor(s) of the investigated prenatal risk factors was significantly ($P < 0.05$) higher in the positively screened LBW subgroup. Many of the individual prenatal risk factors, as well as delivery by Cesarian section (CS) and neonatal ICU admission, occurred more frequently among the positively screened children, but gestational bleeding was the only individual factor that reached statistical significance ($P < 0.05$) (Tables 3 and 4). With regard to the frequency of investigated postnatal risk factors, none showed a statistically significant difference between the two subgroups.

On analysis of the correlation between the M-CHAT scores and the different demographic and clinical data in the 11 positively screened LBW children, M-CHAT scores showed a significant ($P < 0.05$) positive correlation with maternal age at conception ($r = 0.66$) and a tendency ($P = 0.054$) to be positively correlated with paternal age at conception ($r = 0.59$). The scores also showed significant ($P < 0.05$) negative correlations with birth weight, social age, and language age ($r = -0.65$, -0.86, and -0.81 respectively). Meanwhile, no significant correlation ($P > 0.05$) was detected between gestational age and chronological age and M-CHAT scores ($r = -0.38$ and 0.03, respectively).

Discussion

ASDs are being increasingly recognized as an important public health concern [24], and autism is considered one of the most common childhood neurodevelopmental disorders [29]. Onset of unusual behavior often occurs in infancy or in the second year of life [30]. Early intervention has been reported to improve outcome in these children [31]. In 2007, the American Academy of Pediatrics published guidelines recommending screening of all children for autism during their 18 and 24-month well-baby checkups [32,33].

Given the driving goal of facilitating early intervention by improving the early detection of ASD, the M-CHAT has been available for research and clinical use since the late 1990s [19].

In our study, 100 toddlers (24–30 months old) with a history of LBW were screened for autism using the M-CHAT tool in comparison with normal controls. All the LBW children and positive M-CHAT screened controls were then evaluated using CARS, which was reported by Filipek *et al.* [26] to be suitable for use in any child over 24 months of age. This age range (24–30 months) was selected because of the proposal that manifestation of autistic disorder in infancy is more subtle and difficult to define than in those older than 2 years [1]. Robins *et al.* [20] reported that regression is most likely to occur in children between the ages of 15 and 24 months, indicating that children screened at 24 months are not likely to regress after the checklist has been completed.

The current study showed a significantly higher frequency of positive autism screening among LBW toddlers in comparison with the control group. Our finding is comparable to the findings of previous studies, in which a higher risk of infantile autism was seen among children with LBW [34,35]. In addition, Limperopoulos *et al.* [24] found that a higher frequency of children screened positively for autism among extremely LBW infants [24]. LBW is often an indicator of earlier intrauterine effects [36]. It is considered a risk factor for later

Table 2 Comparison between the two low-birth-weight subgroups with respect to the criteria of maturity and birth weight for gestational age

	N (%)		
Variables	Positively screened LBW	Negatively screened LBW	Significance
SGA preterms	3 (27.3%)	5 (5.6%)	$P < 0.05$*
AGA preterms	5 (45.4%)	54 (60.7%)	$P > 0.05$
SGA full-terms	3 (27.3%)	30 (33.7%)	$P > 0.05$

AGA, appropriate for gestational age; LBW, low birth weight; SGA, small for gestational age.
*Significant.

Table 3 Comparison between the two low-birth-weight subgroups with respect to prenatal, natal, and postnatal risk factors

	N (%)		
Variables	Positively screened LBW	Negatively screened LBW	Significance
Prenatal risk factor(s)	8 (72.7%)	29 (32.6%)	$P < 0.05$*
Cesarian section	6 (54.5%)	29 (32.6%)	$P > 0.05$
Postnatal risk factor(s)	5 (45.5%)	20 (22.5%)	$P > 0.05$
Neonatal ICU admission	6 (54.5%)	25 (28%)	$P > 0.05$

LBW, low birth weight.
*Significant.

Table 4 Distribution of different prenatal and postnatal risk factors among the two low-birth-weight subgroups

	N (%)		
Variables	Positively screened LBW	Negatively screened LBW	Significance
Twin pregnancy	1 (9.1%)	2 (2.2%)	$P > 0.05$
Maternal hypertension	2 (18.2%)	7 (7.9%)	$P > 0.05$
Maternal diabetes mellitus	2 (18.2%)	3 (3.4%)	$P > 0.05$
Maternal infection with fever	2 (18.2%)	5 (5.6%)	$P > 0.05$
Gestational drug intake	0 (0%)	3 (3.4%)	$P > 0.05$
Gestational thyroid dysfunction	0 (0%)	2 (2.2%)	$P > 0.05$
Maternal cardiac disorders	0 (0%)	2 (2.2%)	$P > 0.05$
Premature rupture of membrane	2 (18.2%)	4 (4.5%)	$P > 0.05$
Gestational bleeding	3 (27.3%)	5 (5.6%)	$P < 0.05$*
Hyperbilirubinemia	3 (27.3%)	13 (14.6%)	$P > 0.05$
Neonatal infection	1 (9.1%)	4 (4.5%)	$P > 0.05$
Neonatal hypoglycemia	1 (9.1%)	3 (3.4%)	$P > 0.05$

LBW, low birth weight.
*Significant.

neurological and psychiatric problems because it is likely an indicator of fetal growth problems and has been associated with prenatal risk factors, intrapartum complications, and neonatal diseases [37].

In our study, birth weight was found to be significantly lower in LBW infants with positive autism screening than in those negatively screened, whereas gestational age did not show significant difference. However, being SGA in addition to prematurity showed significantly higher frequency in the positively screened subgroup compared with the negatively screened subgroup. Similarly, it was proposed by previous studies that, similar to LBW, gestational age and particularly being small for gestational age were associated with adverse health outcomes, including developmental delays and later intellectual impairments during childhood and adolescence [38,39]. Investigation of pregnancy risk factors in autism has been conducted in a variety of studies, but the associations between autism and birth weight, prematurity, and the related measure of SGA status are inconsistent, in part because of methodological differences and limitations in some studies such as use of small clinic-based samples and lack of control for confounding factors [28].

In our study, we have identified some factors that seem to increase the risk for positive M-CHAT screening for autism, including LBW, higher maternal age, higher paternal age, having one or more prenatal risk factor(s), and having gestational bleeding as a specific prenatal risk factor.

Advanced maternal age is one of the most frequently studied risk factors of autism that was found to be associated with increased risk for autism. This can be explained by the fact that older mothers have an increased risk for obstetric complications possibly because of uterine muscle dysfunction and diminished blood supply with age [40]. It was reported by previous studies that the risk for infantile autism was increased in mothers older than 35 years [34,35] and was also associated with advanced age in either parent [9] and that both advanced paternal (>39 years) [41] and maternal ages emerged as significant predictors of autism and ASDs [10].

Having prenatal risk factor(s) was associated with an increased risk for positive M-CHAT screening in contrast to having postnatal risk factors in our study. Suboptimal conditions during pregnancy and birth have been suggested as a cause of infantile autism [34]. A previous review article by Kolevzon et al. [10] reported that autism is associated with certain perinatal and obstetric conditions. They found significant association between autism and obstetric conditions that included LBW and low gestation duration as well as hypoxia during childbirth. Although this association does not demonstrate a causal relationship, an underlying cause could explain both autism and these associated conditions [10].

Gestational bleeding as a prenatal risk factor was significantly more frequent in the positively screened subgroup compared with the negatively screened subgroup in our study. This finding was comparable to the results of the study conducted by Juul-Dam et al. [42], who found a significantly higher incidence of uterine bleeding than of the other risk factors among their autism group. Bleeding during pregnancy was also included as a risk factor for autism, as reported by Gardener et al. [9],

and a higher incidence of uterine bleeding was also reported in previous studies [43–45]. The possible explanation of the relationship between maternal bleeding and autism is the role of the former in causing fetal hypoxia [9]. Although some brain abnormalities observed in individuals with autism may reflect a potential role of oxygen deprivation during development, this possibility requires further examination. Hypoxia has also been shown to increase dopaminergic activity, and there is evidence for dopamine overactivation in autism [4].

Different investigated prenatal risk factors in our study (twin pregnancy, hypertension, diabetes mellitus, maternal infection with fever, and premature rupture of membranes) showed higher frequencies in positive screeners than in negative screeners, but with no statistical significance. This might be explained by the small number of positively screened LBW children ($n = 11$) compared with the negatively screened children ($n = 89$). However, collectively, metabolic conditions including diabetes, hypertension, and obesity were associated with a higher likelihood of ASD and developmental delay relative to controls in the study by Krakowiak *et al.* [46]. In addition, gestational diabetes was considered a significant risk factor for autism – with two-fold increased risk – by a previous meta-analysis [9]. In contrast, no association was found between autism and maternal diabetes or being a twin in the study by Hultman *et al.* [47]. Meanwhile, episodes of infections and fever and use of antibiotic medications were not found to be associated with infantile autism in the study by Maimburg and Væth [34]. However, exposure to prenatal infections has been suggested to cause deficiencies in fetal neurodevelopment, and early prenatal viral infection has been hypothesized to increase the risk for ASDs [48].

In our study, none of the mothers of toddlers with positive autism screening had a prenatal history of thyroid dysfunction. However, in 2008 Sullivan [49] reported that thyroxin deficiency in the mother during weeks 8–12 of pregnancy produced changes in the fetal brain leading to autism.

Maternal prenatal medication intake was also considered a prenatal risk for autism in the meta-analysis by Gardener *et al.* [9], especially the use of psychiatric drugs. However, in our study, drug intake did not show significant difference as a risk factor for autism on comparing positively and negatively screened children. This variable finding may be attributed again to the small sample of children included in our study or to the types of medicines used, which were not analyzed.

Our study showed that the LBW subgroup with positive autism screening was more frequently delivered by CS and more frequently admitted to the neonatal ICU than was the negative screened subgroup. However, neither of these two factors was statistically significant. This higher frequency of CS delivery in positive screeners might be explained by the increased frequency of the different comorbid prenatal and natal risk factors that might induce hypoxia. Planned CS was considered a risk factor

for pervasive developmental disorders (PDD) in the study by Guinchat *et al.* [50]. CS was also associated with a 26% increased risk for autism that did not reach statistical significance ($P = 0.06$) in the meta-analysis of risk factors for autism performed by Gardener *et al.* [51] and was reported as a risk factor for autism being believed to be related to hypoxia [9]. Intrauterine and neonatal factors related to deviant intrauterine growth or fetal distress were considered important in the pathogenesis of autism [46]. In addition, transfer to neonatal ICUs was a feature among children with infantile autism [34]. However, Gardener *et al.* [51] mentioned that there is insufficient evidence to implicate any one perinatal or neonatal factor in autism etiology, although there is some evidence to suggest that exposure to a broad class of conditions reflecting general compromises to perinatal and neonatal health may increase the risk.

Although the investigated postnatal risk factors (neonatal infection, hypoglycemia, and hyperbilirubinemia) in our study were more frequent among positively screened children than among negatively screened ones, none of them showed statistical significance. In the literature, the epidemiologic evidence for any specific postnatal environmental exposure leading to ASD is scant [6]. Intrauterine or perinatal exposures to infectious, immune, or other environmental factors are proposed as primary mediators of central nervous system damage in neuropsychiatric syndromes; however, the mechanisms and pathogenic basis are not well understood [52]. Although several studies have reported no association between hyperbilirubinemia and autism [44,53–56], a few have suggested that hyperbilirubinemia occurs more frequently than expected among children diagnosed with autism [56]. The study by Juul-Dam *et al.* [42] detected significant associations between both autism and pervasive developmental disorder not otherwise specified (PDD-NOS) and hyperbilirubinemia. Hyperbilirubinemia was also identified as a risk factor for PDD and autism by Guinchat *et al.* [50] and Gardener *et al.* [51], respectively It was proposed that brain plasticity may still allow for postnatal factors to affect the natural history of disease [6]. However, despite evidence of the association of some prenatal, perinatal, and neonatal risk factors associated with PDD, it remains unclear whether these risks are causal or play a secondary role in shaping the clinical expression in individuals with genetic vulnerability [50].

The persistence and pervasiveness of communication and socializing deficits differentiate children with autism from those with specific developmental language disorders [57]. Our study showed that M-CHAT scores of LBW children screened positively correlated significantly with lower language and social ages. These findings are reasonable because autism affects both social and language abilities. Our findings are comparable to the finding of Limperopoulos *et al.* [24], who showed that social age correlated with abnormal M-CHAT scores.

Of the 13 children with positive M-CHAT in the two studied groups (LBW and control), six (46.2%) had CARS

scores that confirmed the diagnosis of autism. Fifty percent of the children with positive CARS had severe autism and the remaining had mild-to-moderate autism. All the negatively screened children in the LBW group were nonautistic as they had CARS scores less than 30. CARS is one of the long-standing and frequently used measures of autism [58]. It is a particularly useful instrument that can provide descriptive information on the pathological behavior of autistic children and the degree of severity [25]. The CARS scale is effective in differentiating individuals with autism from individuals with other disorders in a population with developmental disorders when referring exclusively to autistic disorder in the strict sense of the term. Meanwhile, CARS does not clearly differentiate to the same degree individuals with other ASDs such as Asperger's Disorder and PDD-NOS from individuals with other developmental disorders (nonautistic) [25]. Finally, we can speculate that CARS can be used for definitive autism diagnosis in those children with positive autism screening and for further follow-up of children diagnosed with autism.

Conclusion

LBW is probably an independent risk factor that is associated with the development of autism. Early screening for autism could be recommended for this population especially if they have recognizable prenatal or postnatal risk factor(s) or early impairment of social and language abilities, to be followed by definitive autism testing for those with positive screening results. The M-CHAT should be highlighted as a simple and easily applicable early screening tool that would take about 10 to 15 min to be answered by parents. Meanwhile, the CARS, which is a more time-consuming interview and observation instrument, should be reserved as a confirming method for those with positive screenings. Therefore, it is highly advised to provide M-CHAT as a valuable standard practice checklist in 24-month checkups for toddlers with a history of LBW, aiming at improving the early detection of autism, which may help increase the success rate of early intervention for autism.

Acknowledgements

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