Primitive Reflexes in Very Low Birth Weight Infants Later Diagnosed with Autism Spectrum Disorder

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Abstract

Background: As early screening and diagnosis is very important in treatment of Autism Spectrum Disorder, we investigated the relationship between primitive reflexes and Autism Spectrum Disorder (ASD).

Methods: Of 88 very low birth weight infants born from April 2010 to March 2012, subjects comprised 38 examined for 18 primitive reflexes between age 38 and 45 wks corrected age and followed-up over 6 yrs. ASD was diagnosed using Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) and Autism Diagnostic Observation Schedule Second Edition (ADOS-2). We compared the number of abnormal primitive reflexes between two groups (11 children with and 19 without ASD) after excluding eight children with cerebral palsy in this case-control study.

Results: The number of abnormal primitive reflexes differed significantly between groups, with hypoactive reflexes markedly higher in the ASD group (p=0.001). Conclusion: The result suggests primitive reflexes can be one of the key elements to identify ASD in low birth weight infants. Abnormal primitive reflexes of low birth weight infants with ASD in very early infancy may inform future research of the pathogenesis of ASD.

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction and restricted repetitive patterns of behavior, interests, and activities. The prevalence of ASD has increased over time, particularly since the late 1990s [1]. Recent studies reported prevalence rates of 1.46% in Mainland U.S.A. [2] and 2.64% in South Korea [3]. Although ASD is not fully understood, it is likely that interactions between genes are responsible for ASD and that epigenetic factors and exposure to environmental modifiers contribute to its variable expression [4]. As there is no cure at present, treatment for ASD focuses on behavioral and educational interventions targeting the core symptoms [5]. Especially identification and intervention as early as possible are very important to decrease core symptoms and subsequent behavioral problems [6, 7]. However, prospective longitudinal studies of infants at risk for ASD have generally not observed behavioral signs of ASD until the second year of life [8].

Although motor deficits are not definitive features for diagnosis of ASD, they are common in children with ASD. Approximately 80 percent of teenagers with ASD have definite motor impairment, judged by performance on the Movement Assessment Battery for Children [9]. As for motor development in infancy, a review on general movements (GMs) found of 25 infants later diagnosed with ASD, three showed normal, seven abnormal, 15 absent writhing GMs aged 2 months old or younger, and 17 showed abnormal fidgety GMs between age 3 and 5 months [10].

Primitive reflexes are usually regarded as brainstem mediated, highly stereotypical automatic movement patterns elicited by specific sensory stimuli. Primitive reflexes begin to emerge as early as 25 weeks

gestation and remain clinically evident through 3 to 6 months old. In contrast, postural reactions are regarded as automatic movement patterns with cortical integrity elicited by multiple input modalities and absent neonates [11, 12]. There have been few studies of primitive reflexes and postural reactions in infants with ASD and there is no report of full-term or preterm infants especially within 1 to 2 months actual or 1 to 2 months corrected age as far as the authors know. Similarly, there has been little research in 3 to 11-month-old infants with Autism and Asperger syndrome whose primitive reflexes and postural reactions are not inhibited or fail to appear when they should. But they did not describe their birth weight and gestational age at birth [13, 14]. The authors of these previous studies inferred the possibility of a relationship between abnormal primitive reflexes or postural reactions and the limbic system and/or cerebellum. Research on postures of high-risk infants for ASD aged 3 to 6 months was indicated and two clusters of high and low level of symmetry were reported [15]. The previous authors hypothesized the cerebellum pathway may play an important role in the control of balance and symmetry.

Considering the reports described above, we hypothesized the possibility that early motor signs of ASD may include abnormality of primitive reflexes in very low birth weight infants at corrected age early infancy.

Methods

Participants and data collections

Participants of this case-control study were 88 very low birth weight infants (below 1500 g) who were born and admitted to our hospital from April 2010 to March 2012. Seven who died in Neonatal Intensive Care Unit, seven transferred to other hospitals, 13 discharged before 38 weeks corrected age, one with congenital neurological disease and two unavailable to Brazelton neonatal behavioral assessment (NBAS) due to their physical condition were excluded. Of the remaining 58, 44(76%) were started in the study but we lost 14 infants discharged sooner than anticipated. We report on 38 subjects (17 male, 21 female) of 44 who could be followed-up over six years. As cystic periventricular leukomalacia, Grade III-IV intraventricular hemorrhages by Papile classification and ventriculomegaly are well documented to be associated with adverse neurodevelopmental outcomes, we investigated the results of ultrasound and Magnetic Resonance Imaging of the head. There were no case with these conditions except for cases with cerebral palsy. Primitive reflexes were evaluated between 38 and 45 weeks corrected age as part of NBAS. Primitive reflexes are one of the seven clusters of NBAS which include, orientation, motor, range of state, regulation of state, autonomic stability and reflexes. Evaluation was performed by two trained examiners accredited by the Brazelton Institute (Harvard Medical School, Boston). They inter-rater reliability of the two examiners was 0.885 (κ coefficient). Infants were assessed between feedings, in a small, semi-dark, quiet room with their parent(s). Reflexes included 18 items scored as follows: 0(not elicited despite several attempts), 1(hypoactive response), 2(normal response), 3(hyperactive or obligatory response). Each reflex was ascribed a precise definition for scoring. Reflexes scored 0, 1, or 3 were considered abnormal except for ankle clonus, asymmetric tonic neck reflex and nystagmus (after

tonic deviation of head and eyes). As these three items are often scored 0 or 1, only 3 was regarded as abnormal for these items.

This study has potential selection bias under the two conditions, administration of NBAS after 38 weeks corrected age, and 6 years follow-up period. These conditions might have excluded infants who were discharged early and those whose parents were not worried about the development of their children.

Diagnosis of ASD was made according to DSM-5 at around 3 years old by a child psychiatrist (the first author). There are two main criteria for ASD on DSM-5, one is social communication and social interaction and another is restricted and repetitive patterns of behavior, interest or activities and hyper- or hypo-reactivity to sensory input. We labeled the criteria as S for the former and R for the latter. ASD diagnosis was made when all of three S items were present and more than two of four R criteria were present. Autism Diagnostic Observation Schedule Second Edition (ADOS-2) was also administered to nine of 13 children (four were unavailable to this instrument because three relocated and one had a visual and hearing disability) with ASD diagnosed by DSM-5 and five of 25 without ASD between the age of 5 to 8 years old to qualify the diagnosis. There are two domains for ADOS-2, one is Social Affect and the other is Restricted and Repetitive Behaviors. Final three levels diagnostic classification from the scores of two domains were Autism, Autism spectrum, non-Autism spectrum. ADOS-2 was administered by two accredited examiners (the first and second authors) who scored 0.87 (κ coefficient) for interrater reliability. We compared the numbers of abnormal reflexes between the two groups, infants with and without ASDs. We also investigated correlations between the number of applicable items for ASD diagnosis in DSM-5 or the scores of ADOS-2 and the number of abnormal primitive reflexes.

Statistical analysis

As most of the data had a skewed distribution, a non-parametric statistical test (Mann-Whitney) was used to assess differences in the demographic data and numbers of abnormal primitive reflexes between with and without ASD groups.

SPSS ver.24 was used to perform statistical analyses. P value $P < 0.05$ was considered statistically significant.

Results

Group characteristics

The demographic characteristics of the two groups are shown in Table 1. Only APGAR score (5 min) was higher in infants later diagnosed with than without ASD

The number of abnormal primitive reflexes and their characteristics

The characteristics of primitive reflexes are shown in Table 2. Except eight infants with cerebral palsy, 20 showed one to four hypoactive reflex(es). Ten out of 20 cases were diagnosed with ASD and had one to four abnormal reflex(es). The total number of abnormal reflexes of the 10 ASD cases without cerebral palsy was 25. Twenty-three of 25 abnormal reflexes were hypoactive. Two (cases 6 and 10) out of the 20 infants who had hypoactive reflex(es) also showed hyperactive or obligatory reflex(es) and were diagnosed with ASD. There was a significant difference in the number of abnormal primitive reflexes between the two groups after excluding eight cases with cerebral palsy($p = 0.001$) (Fig. 1).

Discussion

In our study, except for infants with cerebral palsy, the number of abnormal primitive reflexes was significantly higher in infants with ASD aged 38 to 45 weeks corrected age and abnormal primitive reflexes in ASD were mainly weak (23/25).

While hyperactive or obligatory primitive reflexes in the neonatal period are considered indicators of risk for cerebral diseases, absent and hypoactive primitive reflexes are considered indicators of risk for hypotonic cerebral palsy, spinal cord injury or peripheral neuromuscular disease [16]. But many studies reported the predictive power of primitive reflexes for cerebral palsy in infants aged 1 month was low [17, 18].

In contrast, the incidence rates of weak or incomplete primitive reflexes in full-term infants at around birth have been reported as about 36% in walking, 16% in standing, and 7% in placing, after excluding infants with asphyxia [19], 15% in Galant reflex after excluding infants with cerebral palsy and intellectual disability [20]. And one study revealed some primitive reflexes (lower extremity placing reflex, Galant reflex, positive support, steeping reflex) could be weak or incomplete even at 40 weeks corrected age in pre-term infants and, although the main trend of the primitive reflexes became stronger and more complete with increasing corrected age. Those studies did not follow-up developmental prognosis.

Based on our research and previous reports mentioned above, we suspect abnormal primitive reflexes of full-term infants at around term or of preterm infants at around 40 weeks corrected age may indicate some developmental disorders including not only neuromuscular disorders as cerebral palsy but other developmental disorders as ASD.

Why did infants with than without ASD show more abnormalities in primitive reflexes? Primitive reflexes are considered to be mediated by the brainstem, and gait and movement develop thorough bidirectional connections among the cerebrum, cerebellum and midbrain [21, 22].

Although the pathogenesis of ASD is not fully understood, the general consensus is that ASD is caused by genetic factors that affect brain development, specifically neural connectivity. From the neuroanatomical view, candidates for causality of ASD seem to include the cerebellum, cerebrum (frontal and temporal lobe), amygdala, corpus callosum and brainstem. No one has demonstrated essential and consistent evidence of indicators for onset of ASD mainly due to heterogeneity of ASD diagnosis and the

possibility of the developing trajectory of the brain and compensatory structural changes [23–25]. Some researchers have reported brainstem dysfunction in children with ASD by administrating auditory brainstem evoked responses or by the polyvagal theory [26–28].

Taking all of the above into account, abnormal primitive reflexes within the first 6 weeks corrected age in low birth weight infants with ASD might indicate some dysfunction in the cerebellum or brainstem which are strongly related to primitive reflexes and motor development in very early infancy. We believe two important points need to be addressed in our future research. One is to evaluate the precise hypoactive pattern of primitive reflexes and the trajectory of abnormal primitive reflexes in very low birth weight infants. The second determining is how to differentiate ASD from various neuromuscular or other developmental disorders by primitive reflexes with or without combinations of genetic, neuro-functional or movement assessment by increasing the number of study subjects.

This study has some limitations. One is potential selection bias stated in the METHOD section. Another is the small number of subjects. A third is the lack of the data on full term infants with or without ASD. And finally, these findings in very low birth weight infants may not generalize to other infants.

Conclusion

As early intervention is promising in treatment of ASD, early screening and diagnosis is very important. Our study showed the possibility that primitive reflexes of very low birth weight infants at 1 to 2 months corrected age might indicate early signs of ASD. Abnormal primitive reflexes in low birth weight infants with ASD may inform future research of the pathogenesis of neuroanatomical and neurofunctional aspects and the correlation between ASD and motor impairment often coexisting with ASD.

Abbreviations

ASD: Autism Spectrum Disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders fifth edition; ADOS-2: Autism Diagnostic Observation Schedule Second Edition; GMs: general movements; NBAS: Brazelton neonatal behavioral assessment

Declarations

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Availability of data and materials

Data will not be shared because our data are extracted from a clinical database and the ethics committee allows us only an anonymous utilization.

Authors' contributions

Dr.YN has made the examination of NBAS, the acquisition of data, analysis and interpretation of data and discussion writing. Dr.KN has made the examination of NBAS and multidimensional interpretation of data. Dr. OU has made intellectual contributions to clarify conception and design of this study and to help the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The research protocol was approved by the Ethics Committees of Japanese Red Cross Nagoya Daini Hospital.

All parents of the infants gave informed consent to take part in this study and the publication of the data.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

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Figures

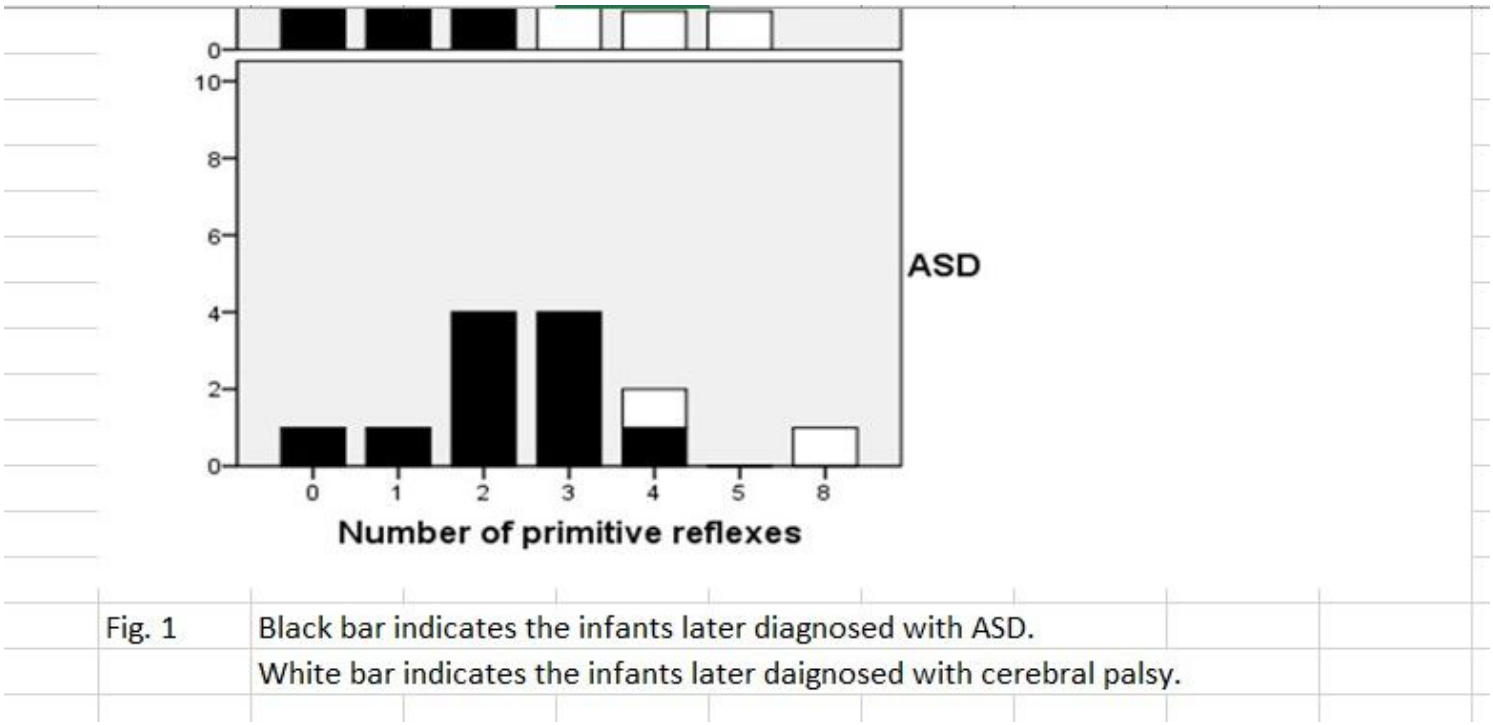

Figure 1

Number of primitive reflexes Black bar indicates the infants later diagnosed with ASD. White bar indicates the infants later diagnosed with cerebral palsy.

Supplementary Files

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