Case Report

Global developmental delay in a child with asphyxia neonatorum: Why search for an additional explanation?

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ABSTRACT

Children presenting neurological problems and a history of "not cried immediately at birth" are labeled to have cerebral palsy due to birth asphyxia. Although this may be true in many situations, the presence of some additional features may help determine an alternate diagnosis. We present such a case with an alternate diagnosis. A child with a history of birth asphyxia was labeled as a case of global developmental delay or a case of cerebral palsy by the treating doctors. However, the child had certain dysmorphic features such as bulbous nose, depressed nasal bridge, low-set ears, high-arched palate, squint, and flat feet. The child was initially treated in the Neonatal Intensive Care Unit after birth. Later, she developed various neurological features, with frequent episodes of aspiration pneumonia and seizures which were managed with anticonvulsant drugs and antimicrobial agents. She also had some additional non-specific features. On detailed evaluation, the child was diagnosed to have 1q43q44 microdeletion. Search for an alternate or additional diagnosis should be carried out if a child presenting with global developmental delay has some additional syndromic features. This will help in the prognostication of child and help parents in future pregnancy.

Key words: Birth asphyxia, Cerebral palsy, Chromosome 1q43q44 microdeletion syndrome, Global developmental delay

Infants and children with neurological manifestations and a history of "not cried immediately after birth" are diagnosed to have cerebral palsy or a case of global developmental delay secondary to birth asphyxia and provided care accordingly. We report such a case with additional manifestations that prompted an additional/alternate diagnosis. It is important to determine accurate diagnosis for instituting appropriate care and clarify the prognosis. Deletion of the sub telomeric region of the long arm of chromosome 1 (1q43q44) is associated with complex neurological phenotype, including moderate-to-severe intellectual disability (ID), microcephaly, epilepsy, and anomalies of corpus callosum [1]. The manifestation of above genetic disorder is complex and can present as a case of global developmental delay. Evaluation of such case can be done if there are associated additional features. We reported such a case, which presented as a case of global developmental delay, but the association of additional features prompted us to look for additional diagnosis which helped us in instituting appropriate care and clarify the prognosis.

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CASE REPORT

A 54-month-old girl born of a non-consanguineous union with developmental delay and a history of "birth asphyxia" presented with the complaints of cough and fever for 5 days. She was already diagnosed as a case of cerebral palsy with global developmental delay, epilepsy, strabismus, hearing impairment, and hypothyroidism and was receiving levetiracetam and sodium valproate, physiotherapy, and thyroxine.

On history and review of records, it was noted that the child was born at term (38.3 weeks, birth weight 1375 g) to a 39-year-old mother through an emergency LSCS (done in view of fetoplacental insufficiency). The child did not cry at birth warranting bag and mask ventilation and required intensive care including non-invasive ventilation subsequently. She developed one episode of generalized tonic–clonic seizures on day-2 of life (D2). A two-dimensional echocardiography carried out in view of a heart murmur showed the presence of a 3 mm patent ductus arteriosus and a 4 mm atrial septal defect (ASD). The child was diagnosed as a case of hypoxic ischemic encephalopathy (HIE) with neonatal seizures, hypothyroidism, and congenital heart disease with single umbilical artery and was discharged on D28 on nasogastric feeds, physiotherapy,

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anticonvulsant (name not known), vitamin supplements, and thyroxin.

Due to problems in swallowing, the child was continued on nasogastric feeds till 2 years of age. During infancy and childhood, she was seen by multiple pediatricians for delayed development and multiple episodes of seizures and aspiration pneumonia. The episodes of pneumonia were treated with anti-microbial therapy, and seizure disorder was treated with long-term anti-convulsant therapy (levetiracetam and phenytoin followed by levetiracetam and valproate).

The electroencephalogram showed right focal seizure temporo-occipital region activity and the magnetic resonance imaging brain showed a paucity of periventricular white matter with prominence of lateral, 3rd, and 4th ventricles. The cerebrospinal fluid spaces along bilateral frontoparietal and temporal cerebral convexities were prominent, and the corpus callosum was thinned. The brainstem-evoked response audiometry demonstrated mild loss at lower frequencies and visual-evoked potential were normal. Abdominal radiograph (KUB), barium swallow study, and ultrasonography of the abdomen did not reveal any abnormality. The echocardiography at 2.5 years of age showed small ostium secundum ASD.

On examination, the child demonstrated growth failure (weight 10 kg [below -3SD], length 85.5 cm [below -3SD]), microcephaly (head circumference: 40 cm, [below 3SD]), dysmorphism (bulbous nose, depressed nasal bridge, low-set ears, and high-arched palate), convergent strabismus (esotropia), hypotonia, hyperextensible joints, bilateral flat feet, and global developmental delay with the developmental age of 3 months across gross and fine motor, social, and adaptive domains. She also demonstrated behavioral problems in the form of inappropriate irritability and obsessive–compulsive behavior.

Although the most of the neurological manifestations and the growth failure could be attributed to HIE and its complications, the additional somatic abnormalities and the presence of cardiac anomalies could not be explained and pointed toward the presence of a chromosomal anomaly. The chromosomal microarray (CMA) study showed chromosome 1q43q44 microdeletion and gain of chromosome 8 at cytoregions p23.3p23.1 (11.4 Mb), indicating trisomy for this region, the latter resembling 8p23.1 duplication syndrome. Parental chromosomal analysis could not be done as the parents refused to undergo any investigations, as they were not keen on future pregnancies.

DISCUSSION

This communication describes a child with growth failure, developmental delay, epilepsy, multiple episodes of pneumonia that were attributed to cerebral palsy secondary to perinatal asphyxia. However, chromosomal analysis study prompted by the presence of several associated physical manifestations revealed the presence of chromosome 1q43q44 microdeletion (OMIM 612337), and trisomy of chromosome 8 at the cytoregion p23.3p23.1.

This case illustrates the not-so-uncommon phenomenon of the treating doctors discontinuing further evaluation once a diagnosis explaining most of the manifestations is reached. For example, in this case while most of the neurological manifestations (developmental delay, microcephaly, epilepsy, feeding difficulties, and mild hearing impairment) and other features such as repeated episodes of aspiration pneumonia and growth failure could be easily explained by HIE and its complications, the presence of facial dysmorphism, other somatic abnormalities, and heart disease should have prompted additional evaluation.

Chromosome 1q43q44 microdeletion occurs with a frequency of <1 per million live births [1]. Only 230 cases of chromosome 1q43q44 or 1q44 microdeletion have been described worldwide [2], none from India. The nonspecific nature of manifestations associated with the microdeletion 1q43q44 (craniofacial dysmorphism, dysphagia, short stature, and global developmental delay) may be responsible for many cases being missed [2]. Facial features which are commonly seen in this syndrome include microcephaly (90% cases) [3], round face, thin upper lip with prominent cupid bones, thin downturned coarse of mouth, short nose with broad root, strabismus, tele–canthus, and low set ears [2]. Other features reported with chromosome 1q43q44 microdeletion include seizures (75%) [2], absence or hypoplasia of corpus callosum (90%) [2], hydrocephalus (30%) [3], heart defects (30%) [3], hearing impairment (15%) [3], ID, short stature, and skeleton abnormalities [2,4,5]. As one can see, there is a significant overlap between the manifestations of the microdeletion syndrome and those resulting from HIE and its complications. However, facial dysmorphism and structural abnormalities in multiple organs (e.g., thinning of the corpus callosum and heart defects) should provide clues for the need for additional evaluation. Several genes in the 1q44 locus are known to be associated with microcephaly and seizures [2]: Haploinsufficiency of AKT3 gene leads to microcephaly, agenesis of corpus callosum, and other brain developmental abnormalities [1,2,6]; ZBTB18 gene and HNRNPU cause abnormalities of the corpus callosum [1,2,6]; mutation in the HNRNPU gene is, also, one of the main causes of ID associated with this syndrome. Loss of function of the HNRNPU and COX20 has been shown to be associated with seizures [7]. Furthermore, the HNRNPU gene mediates the long range control of SHH gene (7q36.3), which is necessary for the development of the brain, eyes, limbs, and other parts of the body [2,8,9].

With the help of CMA, we were able to provide explanation for most of the manifestations. Although hypothyroidism has not been previously reported in cases with the microdeletion, cases reported in the future will help determine if this is an incidental finding. Being a chromosomal microdeletion, no treatment of the cause is possible, and the child was managed symptomatically with the continuation of supportive care. As the parents refused further investigations, parental chromosomal microanalysis that would have helped delineate the risk of recurrence (most cases are secondary to balanced translocation in parents) could not be undertaken.

CONCLUSION

The case report highlights on the fact that not all developmental delay is related to birth asphyxia and if any child presents with some additional features, then one can try to evaluate for alternate cause of developmental delay. In our case, the child had additional features along with developmental delay, hence chromosomal analysis was advised. Furthermore, another reason for this case report is, chromosome 1q43q44 microdeletion occurs with a frequency of <1 per million live births. Only 230 cases of chromosome 1q43q44 or 1q44 microdeletion have been described worldwide, none from India. To our knowledge, this would be the first such case reported in India.

AUTHORS CONTRIBUTORS

Shreyas A. Surpure: Prepared the first draft of the protocol and manuscript, development of publication idea, literature search, approval of the final draft of the manuscript; Bhavesh Rathod: Significant intellectual inputs for the improvement in the protocol and manuscript, supervision over data collection, literature search, and approval of the final draft of the manuscript.

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