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CASE REPORT

A Girl from Canada with Severe Cerebral Palsy Associated with Hydrocephalus and Mutation of Kinase D-Interacting Substrate of 220-kDa (Kidins220) Gene: A New Syndrome with Unique Brain Imaging Findings and a Therapeutic Challenge

Aamir Jalal Al-Mosawi

Baghdad Medical City and the Iraqi Ministry of Health, Iraq

Correspondence should be addressed to Aamir Jalal Al-Mosawi, Baghdad Medical City and the Iraqi Ministry of Health, Baghdad, Iraq

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ABSTRACT

BACKGROUND

Cerebral palsy is a heterogeneous neurologic condition caused by abnormalities of brain development or damage affecting mostly regions controlling movements, balance, and posture. The brain abnormalities and damage causing cerebral palsy are characteristically non-progressive, but lead to permanent abnormalities of movements, posture, and limitation of mobility. Kinase D-interacting substrate of 220 kDa (KIDINS220), a trans-membrane protein that is essential for growth mediating pathways in the nervous system. Heterozygous KIDINS220 truncating variants affecting protein's C-terminus have been reported only in few unrelated children who had spastic paraplegia, mental retardation, nystagmus, and obesity. A homozygous, more N-terminal truncating variant in KIDINS220 gene has been reported to be associated with enlarged brain ventricles and limb contractures in three foetuses from a consanguineous family.

PATIENT AND METHODS

The family of a girl who developed severe cerebral palsy caused by hydrocephalus and had mutation of kinase D-interacting substrate of 220-kDa (Kidins220), consulted us about the possible therapies her condition. Unique brain imaging abnormalities are described, and the relevant literatures were reviewed with aim of suggesting possible evidence-based therapies.

RESULTS

A 33-months old girl from Canada had cerebral palsy dominated by spasticity and caused hydrocephalus. The girl had slight nystagmus and was also thought to experience sometimes dystonia. During the first 18 months of life,

her head was enlarging, and Brain MRI showed dilated lateral ventricles, hypoplastic basal ganglia and inferior vermis, agenesis of septum pellucidum, thin corpus collosum. Before surgery (endoscopic third ventriculostomy) at 19 months of age, her head circumference was above the 99th percentile. Her head stabilized after the surgery. Literature review suggested the possible usefulness of the use multi-factorial therapies including cerebrolysin, citicoline, piracetam, and pyritinol, and based on our extensive clinical experience we suggested an initial one-month therapeutic course.

CONCLUSION

In this paper, a new genetic syndrome is described. The syndrome is associated with mutation of KIDINS220 gene, cerebral palsy, hydrocephalus, nystagmus, and unique brain imaging findings including hypoplastic basal ganglia and inferior vermis, agenesis of septum pellucidum, and thin corpus collosum.

KEYWORDS

New genetic syndrome; Mutation of KIDINS220 gene; Cerebral palsy; Hydrocephalus; Nystagmus

INTRODUCTION

Cerebral palsy is a heterogeneous neurologic condition caused by abnormalities of brain development or damage affecting mostly regions controlling movements, balance, and posture. The brain abnormalities and damage causing cerebral palsy are characteristically non-progressive, but lead to permanent abnormalities of movements, posture, and limitation of mobility [1-4].

We reported the occurrence of various brain imaging abnormalities in children with cerebral palsy including brain atrophy, periventricular leukomalacia, arachnoid cyst, and cerebellar atrophy/cerebellar hypoplasia [5-15].

Kinase D-interacting substrate of 220 kDa (KIDINS220), a trans-membrane protein that is essential for growth mediating pathways in the nervous system. Heterozygous KIDINS220 truncating variants affecting protein's C-terminus have been reported only in few unrelated children who had spastic paraplegia, mental retardation, nystagmus, and obesity.

A homozygous, more N-terminal truncating variant in KIDINS220 gene has been reported to be associated with enlarged brain ventricles and limb contractures in three foetuses from a consanguineous family [16].

PATIENT AND METHODS

The family of a girl who developed severe cerebral palsy caused by hydrocephalus and had mutation of kinase D-interacting substrate of 220-kDa (Kidins220), consulted us about the possible therapies her condition. Unique brain imaging abnormalities are described, and the relevant literatures were reviewed with aim of suggesting possible evidence-based therapies.

RESULTS

The 33-months old girl from Canada was studied during October 2021 (Figure 1). She had cerebral palsy dominated by spasticity and caused hydrocephalus. She had significant delay in gross motor, fine motor, speaking, and was unable to sit unassisted and had poor head control. She was unable to neither roll, crawl, sit, nor stand. Spasticity had already associated with flexion deformity at the ankle which was correctable. However, the child

was able to recognize the face of the mother, and was smiling, and responding to her name. She was starting to make some sounds with words, na, ma. She also had slight nystagmus. The girl was also thought to experience sometimes dystonia.

During the first 18 months of life, her head was enlarging, and Brain MRI showed dilated lateral ventricles, hypoplastic basal ganglia and inferior vermis, agenesis of septum pellucidum, thin corpus collosum.

Figure 1: A 33-months old girl from Canada who had cerebral palsy dominated by spasticity.

Before surgery (endoscopic third ventriculostomy) at 19 months of age, her head circumference was above the 99th percentile. Her head stabilized after the surgery

She was receiving baclofen 10 mg at bedtime, gabapentin, and omeprazole for gastro-oesophageal reflux.

Literature review suggested the possible usefulness of the use multi-factorial therapies including cerebrolysin, citicoline, piracetam, and pyritinol, and based on our extensive clinical experience we suggested an initial one-month therapeutic course [1-15].

The initial therapeutic course primarily aimed at:

1. Improving posture and spontaneous movement by providing adequate muscle relaxation which hopefully results in easier correction of the flexion deformity at the ankle.
2. Repairing brain which can result in improved brain function that can be manifested early by improvement in head control, and sometimes may result an early cognitive improvement which can be associated with improved speech and a better understanding of simple speech. Improvement in nystagmus may occur early.

Our suggested evidence-based treatment included withdrawal of gabapentin, and the gradual increase of baclofen to 20 mg daily in 4 divided doses during the first month of treatment. Initially, Baclofen 5 mg is given three times a day, and increased to 4 times a day on day 8. Diazepam 2 mg daily at bedtime is added at day 14 and continued.

In addition, Cerebrolysin 2 ml given by intramuscular injection daily every other day during the morning hours (15 doses over one month). Oral Citicoline syrup 2 ml (200 mg) daily in the morning was also prescribed.

DISCUSSION

Neuroimaging studies showing enlarged ventricles suggest the diagnosis of hydrocephalus in the presence of head enlargement. However, as early as 1996, the work of Campistol and colleagues suggested that in the absence of macrocephaly, brain images showing slight ventricular dilation, normotensive hydrocephalus, hydrocephalus with irregular limits, subcortical atrophy or periventricular heterotopia may indicate residual periventricular leukomalacia [17].

Bringas-Grande (2002) from Spain reviewed 250 patients with cerebral palsy and reported their brain imaging findings which included atrophy in 38.8%, hydrocephalus in 29.4%, ischemia in 14.9%, haemorrhage in 11.6%, and no abnormalities in 23.8% [18].

Pharoah (2007) from the United Kingdom reviewed patients with cerebral palsy born in 1966-1991 in the counties of Merseyside and Cheshire, UK, and reported an important association between cerebral palsy and hydrocephalus [19].

Rankin et al (2010) reviewed 1104 patients (663 males, 441 females) with cerebral palsy were born during the period from 1991 to 1999 in three areas (Isère Region, French Alps; Funen County, Denmark; Northern Region, England). They found that the most common cerebral anomalies were primary microcephaly which was observed in 26.5%, and congenital hydrocephalus which was observed in 17.3% [20].

Grigore and Diaconu (2010) reported brain MRI and CT-scan findings in 129 children (86 males, 43 females; aged 2 years - 18 years) who had various types of cerebral palsy. 100 patients (77.52%) had CT-scan and 29 patients (22.48%) had MRI. 19 patients (14.72%) had normal MRI and CT-scan. Ventriculomegaly which indicates hydrocephalus in the presence of head enlargement was the most common findings and occurred in 38 patients, followed by focal infarct which was observed in 28 patients, periventricular leukomalacia was observed in 17 patients, cortical and cortical/subcortical atrophy was observed in 13 patients, basal ganglia lesions were observed in 12 patients, and cortical migration and organization problems were observed in 12 patients [21].

Kinase D-interacting substrate of 220 kDa (KIDINS220), a trans-membrane protein that is essential for growth mediating pathways in the nervous system. Heterozygous KIDINS220 truncating variants affecting protein's C-terminus have been reported only in few unrelated children who had spastic paraplegia, mental retardation, nystagmus, and obesity.

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CONFLICTS OF INTEREST

None.

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