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### GESTALT DIAGNOSIS OF CHILDREN WITH DYSMORPHISM - NECESSITY FOR ESTABLISHING GENETIC DIAGNOSTIC APPROACH

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#### ABSTRACT

**Background:** The overall prevalence of intellectual disability is approximately 2-3% in the general population and can be caused by genetic and environmental factors. Genetic factors include chromosomal anomalies, single-gene disorder, deregulation of imprinted genes, and multiple malformation syndromes without an identified genetic basis and idiopathic. In Bangladesh, the genetic diagnosis of dysmorphic patients has not yet been well established. Therefore, gestalt diagnosis has a crucial role in establishing the differential diagnosis, management, counseling and genetic diagnostic approach. **Aim of the study:** The aim of the present study was to assess the effectiveness and necessity of gestalt diagnosis on the suspected genetic syndrome with intellectual disability and comorbidities. **Methods:** This prospective study was conducted at Dhaka Shishu Hospital during the period from December 2017 to May 2018. The study included 21 children with intellectual and developmental disabilities (IDD) who attended OPD and Mental Health Clinic of Dhaka Shishu Hospital, Dhaka, Bangladesh. Elaborate history taking, physical examination, and psychological assessment were done. The dysmorphic features were analyzed and correlated with syndromic diagnosis using OMIM search. Parents were counseled about the preferred genetic diagnostic tests to confirm the syndromic diagnosis. Prognosis of the index children and chance of recurrence in the next pregnancy was discussed when a particular syndrome was suspected.

#### ORIGINAL RESEARCH ARTICLE

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Informed written consent was taken from parents of every patient to use the photograph and data for diagnostic and academic purposes. **Results:** Among total participants, 40% had severe cognitive delay 35% had a moderate delay, 25% had a mild cognitive delay, 70% had behavior problems and 55% had ASD and/or ADHD features. Seizure was present in 35% of patients. Among other comorbidities; speech and language delay were in 65%, motor delay was in 50%, vision impairment was in 10%, hearing impairment was in 15%. Suspected cases were, Noonan syndrome: 4, Angelman syndrome: 3, Fragile X syndrome: 2, Kabuki syndrome: 2, Sotos syndrome: 2. Genetic diagnosis could be established in only 2 patients with suspected fragile X syndrome. **Conclusion:** The study emphasizes the necessity to approach gestalt diagnosis in syndromic children with IDD along with locally available low-cost genetic diagnostic facility thereby increasing the possibility of providing appropriate management and/or genetic counseling.

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## I. INTRODUCTION

The overall prevalence of intellectual disability is approximately 2-3% in the general population and can be caused by genetic and environmental factors. Genetic factors include chromosomal anomalies, single-gene disorder, deregulation of imprinted genes, and multiple malformation syndromes without an identified genetic basis. Others are idiopathic. In Bangladesh, the genetic diagnosis of dysmorphic patients has not yet been well established. Therefore, gestalt diagnosis has a crucial role in establishing differential diagnosis, management, and counseling approach. Gestalt identification is the process through which healthcare practitioners for patients with IDD can actively organize clinical perceptions into specific diagnostic ideas. Through this method, clinicians can generate diagnostic hypotheses simply depending on the combination of specific dysmorphisms features and/or particular elements of the related clinical history very quickly. For instance, Down,<sup>1</sup> Cornelia de Lange,<sup>2</sup> Turner,<sup>3</sup> Noonan,<sup>4</sup> Kabuki,<sup>5</sup> Treacher Collins,<sup>6</sup> Waardenburg<sup>7</sup> and Williams Angelman<sup>8</sup> syndromes are examples where the gestalt features can be readily analyzed by

paediatricians. In 2000, Fridman claimed,<sup>10</sup> ‘This typical evaluation can permit to suspect PWS diagnosis and to perform methylation test for 15q11.2 regions. In like manner, some Paediatric Neurologists suggest that ‘Angelman syndrome’s<sup>9</sup> EEG pattern is typical enough to be recognized by sensitized professional’s. Therefore, to bring an end to the child’s “diagnostic odyssey” that may have included years of uncertainty, anxiety, and evaluations, Mollison L, O’ Daniel JM, et al<sup>11</sup> a genetic diagnosis can provide families with an explanation. Moreover, it can also guide patients and their families to condition-specific resources and supports. Receiving a diagnosis has also been shown to increase knowledge, provide a sense of empowerment, resulting in peace of mind, increase the parental quality of life, Lingen M, Albers L, et al<sup>12</sup> decrease parental guilt, Reiff M, Bernhardt BA, et al<sup>13</sup> and foster increased acceptance. Krabbenborg L, Vissers LELM, et al<sup>14</sup>

## II. OBJECTIVE

### General Objective:

To assess the effectiveness and necessity of gestalt diagnosis on suspected genetic syndrome with intellectual disability and comorbidities.

**Specific Objective:**

- To determine the demographic status of the participants.
- To determine the co-morbidities and features among the participants.

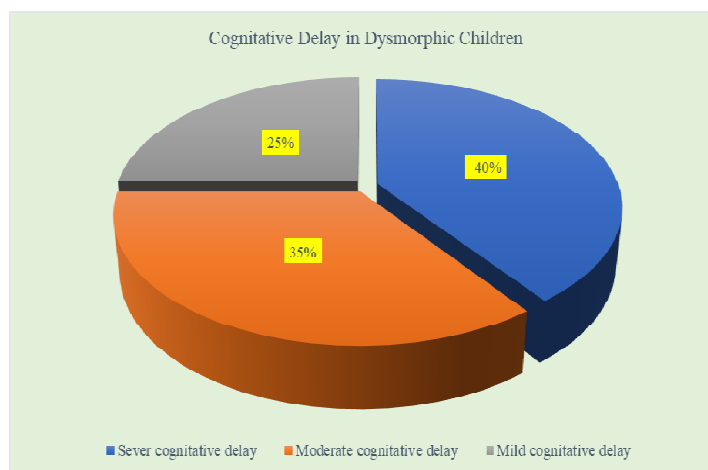
**III. METHODOLOGY**

This was a prospective observational study which was conducted at Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh of 6 months' duration from December 2017 to May 2018. The study included children with intellectual and developmental disabilities (IDD) and several co-morbidities with dysmorphism who attended OPD and the Mental Health clinic of Dhaka Shishu Hospital. Total study people were 21 in number. Elaborate history taking, physical examination, and psychological assessment were done, the dysmorphic features were analyzed and correlated with syndromic diagnosis using OMIM search. Parents were counseled about the preferred genetic diagnostic tests to confirm the syndromic diagnosis. Prognosis of the index children and chance of recurrence in the next pregnancy was discussed when a particular syndrome was suspected. Informed written consent was taken from parents of every patient to use the photograph and data for diagnostic and academic purposes. A pre-designed questioner was used to collect patient data. Data were processed, analyzed, and disseminated by

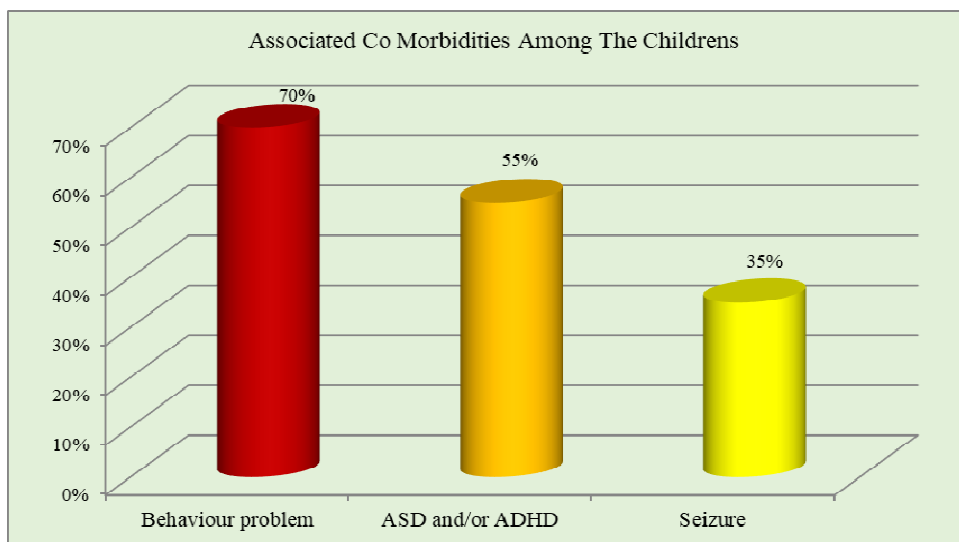
using MS Office and SPSS version 26.0 as per need.

**IV. RESULT**

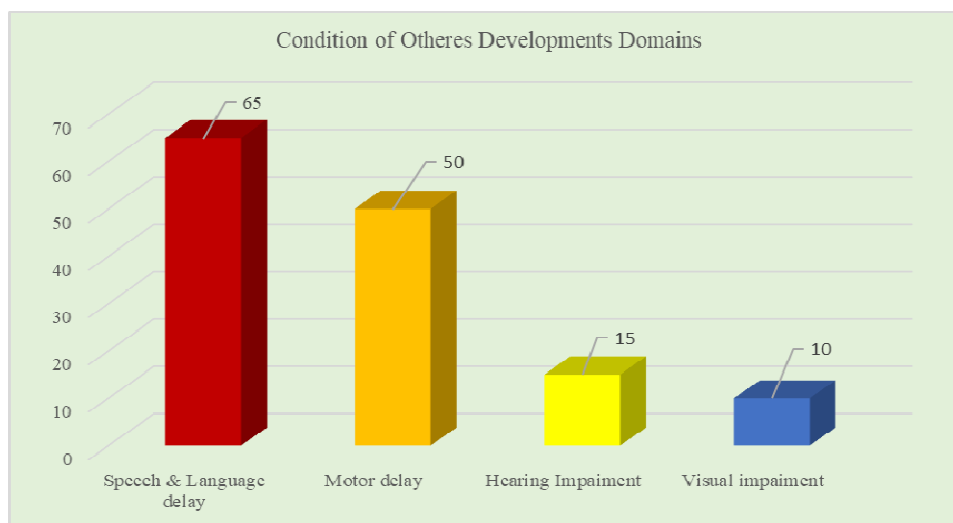
In this study, a total of 21 patients presented with dysmorphism. The mean age of the participants was 7.8 years. Male participants were dominating in number and the male-female ratio was 2.3:1. In analyzing the demographic status of the participants we observed that 70% of participants were from rural areas. In this study, 55% of participants were from middle socioeconomic backgrounds. In total 40% of patients had a severe cognitive delay while 35% had moderate and 25% had a mild cognitive delay. On the other hand, 70% had behavior problems, 55% had ASD and/or ADHD features. Among total study people, the seizure was present in 35% of patients. Among other comorbidities; speech and language delay was in 65%, the motor delay was in 50%, vision impairment was in 10%, hearing impairment was 15%. Besides these, suspected cases were distributed as, Noonan syndrome in 4, Angelman syndrome in 3, Fragile X syndrome in 2, Kabuki syndrome in 2, Sotos syndrome in 2 patients. The remaining are Coffin-Lowry, Potocki-Lupski, Silver-Russel, Waardenburg, Seckel, Laron, Treacher-Collin, and Di-George syndrome. Genetic diagnosis could be established in only 2 patients with suspected fragile X syndrome.



**Figure I:** Distribution of cognitive delay status among participants (N=21)



**Figure II:** Distribution of co-morbidities among participants (N=21)



**Figure III:** Condition of other developmental domains in percentage (N=21)

**Table 1:** Syndromes suspected by analysis of gestalt (N=21)

Characteristics	n	%
Noonan syndrome	4	19.05
Angelman syndrome	3	14.29
Fragile X syndrome	2	9.52
Kabuki Syndrome	2	9.52
Sotos syndrome	2	9.52
Coffin-Lowry syndrome	1	4.76
Potocki-Lupski Syndrome	1	4.76
Silver-Russel Syndrome	1	4.76
Waardenburg Syndrome	1	4.76
Seckel Syndrome	1	4.76

Laron Syndrome	1	4.76
Treacher-Collin Syndrome	1	4.76
Digeorge syndrome	1	4.76



**Picture I:** Teachers Collins Syndrome



**Picture II:** Silver Russel Syndrome





**Picture III:** Noonan Syndrome



**Picture IV:** Kabuki Syndrome



Picture V: Father & Child with Waardenburg Syndrome

## V. DISCUSSION

The aim of the present study was to assess the effectiveness and necessity of gestalt diagnosis on the suspected genetic syndrome with intellectual disability and comorbidities. In our study, a total of 21 patients presented with dysmorphism. The mean age of the participants was 7.8 years. Male participants were dominating in number and the male-female ratio was 2.3:1. In analyzing the demographic status of the participants we observed that 70% of participants were from rural areas. In this study, 55% of participants were from middle socioeconomic backgrounds. There is no systematic study of the benefits (or harms) of a comprehensive evaluation of the child with developmental delays or mental retardation (DD/MR). However, there are recurring statements of likely benefits for parents and patients in the literature, Curry CJ, Stevenson RE, Aughton D, et al.<sup>15</sup> for example, Shevell MI<sup>16</sup> indicated that, the etiologic diagnosis in the young child has immediate implications concerning recurrence risks as well as therapeutic imperatives, possessing the potential to modify management and expected outcomes and that “future medical challenges and the actual prognosis for the disabled child

can be more accurately addressed.” According to Cassel EJ<sup>17</sup> the family of a child with DD/MR often experiences the feeling of a loss of control, and a diagnosis can contribute to the family feeling in control once more. In our study, in total 40% of patients had a severe cognitive delay while 35% had moderate and 25% had a mild cognitive delay. On the other hand, 70% had behavior problems, 55% had ASD and/or ADHD features. Among total study people, t seizure was present in 35% of patients. Among other comorbidities; speech and language delay was in 65%, the motor delay was in 50%, hearing impairment was in 15% and vision impairment was in 10%. Suspected cases were distributed as, Noonan syndrome in 4, Angelman syndrome in 3, Fragile X syndrome in 2, Kabuki syndrome in 2, Sotos syndrome in 2 patients. Genetic diagnosis could be established in only 2 patients with suspected fragile X syndrome. Treacher Collins syndrome is a high penetrance and variable expressivity with an autosomal dominant disorder of craniofacial morphogenesis. It is estimated that the frequency of TCS is 1 in 50,000 live births.<sup>18-20</sup> In Silver Russel syndrome almost all patients are born small for gestational age. By the presence of other characteristic features,

including relative macrocephaly which is defined as a head circumference at birth  $\geq 1.5$  SD score above birth weight and/or length, prominent forehead, body asymmetry, and feeding difficulties. SRS can be distinguished from those with idiopathic intrauterine growth retardation or SGA and postnatal growth failure in children.<sup>21-24</sup> According to a study globally estimated incidence of SRS range is 1: 30,000 to 1: 100,000.<sup>25</sup> However, only molecularly confirmed cases were included, which could have resulted in underdiagnosis. Though the exact incidence remains still unknown, SRS is probably more common than the previous estimation. The reason of child Noonan syndrome is a genetic disorder that prevents normal development of the parts of the body.<sup>26</sup> The symptoms include unusual facial characteristics, short stature, heart defects, possible developmental delays, and other physical difficulties. Although its prevalence has not been accurately determined yet, it is thought to be comparatively common. Most authors cite the figure of 1 in 1,000-2,500 live births according to the study by Nora et al.<sup>27</sup> Kabuki syndrome is a rare syndrome characterized by distinct dysmorphic unusual dermatoglyphic patterns, intellectual disabilities, facial features, postnatal growth retardation, and skeletal abnormalities. It is usually detected sporadically and has a wide spectrum of clinical manifestations.<sup>28</sup> Recently it was identified as a genetic syndrome via whole-exome sequencing,<sup>29</sup> In many cases, KS has been increasingly recognized in the primary care setting. Waardenburg syndrome is a group of genetic conditions inherited in an autosomal dominant fashion.<sup>30</sup> During embryogenesis, there is an abnormal distribution of melanocytes, which results in patchy areas of depigmentation. It is a rare disease, caused by the loss of pigmentary cells in the eyes, skin, stria vascularis of the cochlea and hair.<sup>31</sup> Several different gene mutations cause for Waardenburg syndrome.

Among four clinical variants, type 1 and type 2 are the most common. Type 1 clinically manifests as congenital deafness, neural tube defects, dystopia Cantorum, and patchy depigmentation of hair, skin due to the mutations in the PAX3 gene. It is associated with pigmentary abnormalities of the eyes. And type 2 is mutations in the MITF gene.<sup>32</sup>

#### **VI. LIMITATION OF THE STUDY**

This was a single-centered study with a small sample size. So, the findings of this study may not reflect the exact scenario. Besides this was not a comparative study. So, the claim of just establishing the necessity of a genetic diagnostic approach may have been considered a weak approach.

#### **VII. CONCLUSION & RECOMMENDATION**

The study emphasizes the necessity to approach gestalt diagnosis in syndromic children with intellectual and developmental disabilities along with locally available low-cost genetic diagnostic facility thereby increasing the possibility of providing appropriate management and/or genetic counseling.

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