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Neurodevelopmental Outcome in Children with Down Syndrome

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ABSTRACT

Background: Down syndrome is the most common identifiable genetic cause of intellectual disability and birth defects. Although intellectual disability and hypotonia are present in virtually all individuals with DS, the expression of other DS-associated congenital and acquired medical complications is variable.

Aim of the work: The aim of the study is to determine the neurodevelopmental, behavioral, mentality outcome and associated neurological complications in children with Down Syndrome.

Methods: Forty children with Down syndrome were enrolled from June 2016 to March 2017 in the genetic clinic in Fayoum University Hospital. For all, EEG study was done; evaluation using Portage program, and serum TSH, free T3and free T4 was measured. For selected cases fundus examination, ABR, and MRI was done.

Results: There was significant developmental delay in motor abilities, self-help, social, cognitive, communication, and language skills in our cases. There was a significant relation between motor development, self-help skills, communication skills, language development and head circumference; however, no significant relation was found between cognitive skills and head circumference. There was a significant relation between delay in cognitive skills and EEG abnormalities. There was no significant relation between cytogenetic type of Down Syndrome, presence or absence of cardiac abnormalities, and portage score.

Conclusion: All items of developmental outcome were affected in Down Syndrome. The Portage scores (in motor development, self-help skills, communication skills, language development) were affected by microcephaly and EEG abnormalities were found in cases with cognitive disabilities.

KEYWORDS:Down Syndrome; neurodevelopmental outcomes; EEG changes.

INTRODUCTION

Down Syndrome (DS), also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is typically associated with physical growth delays, characteristic facial features, and mild to moderate intellectual disability **[Weijerman and Winter., 2010].**

The average IQ of a young adult with Down Syndrome is 50, equivalent to the mental age of an 8 or 9 years old, but this varies widely **[Malt et al., 2013].**

Many developmental milestones are delayed **[Rondal et al.,2007].** Newborns with DS may exhibit marked hypotonia that usually

improves during childhood. The low tone causes ligamentous laxity and delays the acquisition of milestones **[Guidi et al., 2011].**

Children and adults with DS are at increased risk of epileptic seizures which occur in 5-10% of children and up to 50% of adults **[Hickey et al., 2012].**

Cardiac defects predispose children with DS to stroke. A classic complication that leads to stroke in children with DS is moyamoya syndrome **[Boggs., 2008].**

Commonly, individuals with DS have better language understanding than ability to speak **[Kent et al., 2013].**

Current prevalence estimates of neurobehavioral and psychiatric comorbidity in children with DS range from 18% to 38%. Included in this category are depression, and ADHD, The incidence of autism spectrum disorders (ASD) in patients with DS has been reported to be 18% several times higher than that found in the general population **[DiGuiseppi et al.,2010].**

PATIENTS AND METHODS

This study was cross sectional descriptive study and conducted in the genetic clinic of Fayoum University Hospital. Forty children with Down syndrome were enrolled from June 2016 to March 2017. All cases were subjected to the following :

-Full history taking including family history as maternal age at birth of the case, similar conditions in the family, antenatal risk factors.

-Clinical examination of all body systems including full neurological assessment, cardiac, respiratory, abdominal, and genital systems focusing on associated anomalies.

-Evaluation of body weight, height, and head circumference using Growth Charts for normal child and for Down children.

-Laboratory investigations such as:

•TSH, Serum free T3and free T4 for detection of hypo-or hyperthyroidism.

-Other investigations according the detected problem (fundus examination for cases of nystagmus, MRI was done for cases with nodding and cases with nystagmus, and ABR for cases with decreased hearing acuity).

-Echocardiography was done to all patients.

-Written consent from all patients was taken.

RESULTS

Table (1): Relation between height on percentiles of normal and of down children:

		Percentiles of normal children				P-value
		Below 3rd		Normal		
		N	%	N	%	
percentiles of Down children	**Below 5%**	5	50.0	0	0.0	<0.0001*
	Normal	5	50.0	23	76.7	
	Above 95%	0	0.0	7	23.3	

Head circumference measurements, percentiles of normal children showed that 14 out of 40 (35%) of patients were below the third percentile and the other 26 (65%) were normal , percentiles of Down children showed that 6 patients (15 %) were below 5th percentile, 3 patients (7.5%) were on 5th percentile, and 34 patients (85%) had normal head circumference. This showed a highly significant difference when comparing normal and down percentile for head circumference (P value < 0.0001).

Table (2): Relation between HC on percentiles of normal and of down children:

		Percentiles of normal children				P-value
		Below 3rd		normal		
		N	%	N	%	
Percentiles of Down children	**Below 5%**	6	42.9	0	.0	<0.0001*
	Normal	8	57.1	26	100.0	

Full prenatal history was taken from all participants focusing on the important risk factors that may be related to development of Down syndrome such as consanguinity and maternal age. The mean age of mothers was (32.42±7.04) years old ranged between (19 years and 44 years). It was noted that 40% of Down syndrome patients had history of positive consanguinity. Regarding antenatal history, 17.5% had history of x-ray exposure, 2.5% had gestational hypertension, and 2.5% had history of MRI exposure, 17.5% had a similar condition in the family.

Table (3): Risk factors of Down syndrome (N=40):

Variable	Mean ± SD	Range
Maternal age (years)	32.42 ± 7.04	19-44
Variable	**N**	**%**
Consanguinity:		
Positive	16	40.0
Negative	24	60.0
Antenatal:		
No	31	77.5
Exposed to x-ray	7	17.5
Hypertension with pregnancy	1	2.5
Exposed to MRI	1	2.5
Similar condition:		
Yes	7	17.5
No	33	82.5

Echocardiography revealed that 50% of Down Syndrome patients had cardiac problems (22.5% had ASD, 17.5% had VSD, 2.5% had ASD and VSD, 2.5% Fallot tetralogy, 2.5% tricuspid regurgitation, and 2.5% PFO). ASD was the commonest congenital heart disease, regarding other congenital anomalies 10% had anomalies in the form of umbilical hernia (2.5%), undescended testis (2.5%), imperforate anus (2.5%), and megacolon (2.5%).

Table (4): Distribution of patients as regards congenital anomalies:

Variable	N	%
Cardiac anomalies:		
No	20	50.0
ASD	9	22.5
VSD	7	17.5
ASD & VSD	1	2.5
Fallot tetralogy	1	2.5
Tricuspid regurgitation PFO	1	2.5
Other anomalies:		
Yes	4	10.0
No	36	90.0

Figure (1): The distribution of cardiac anomalies among DS patients

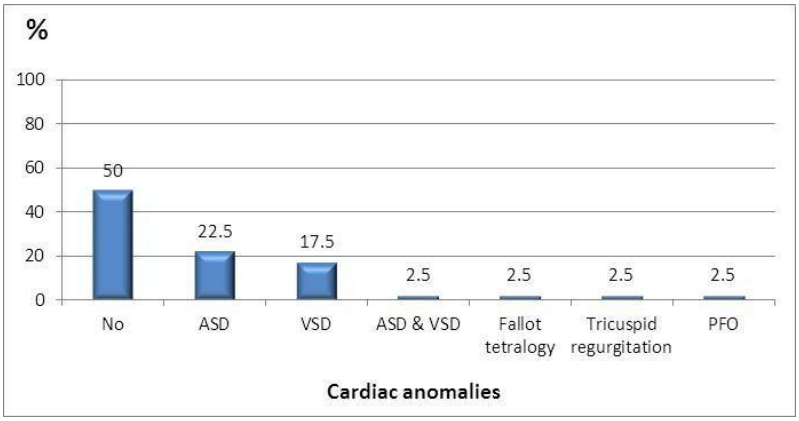
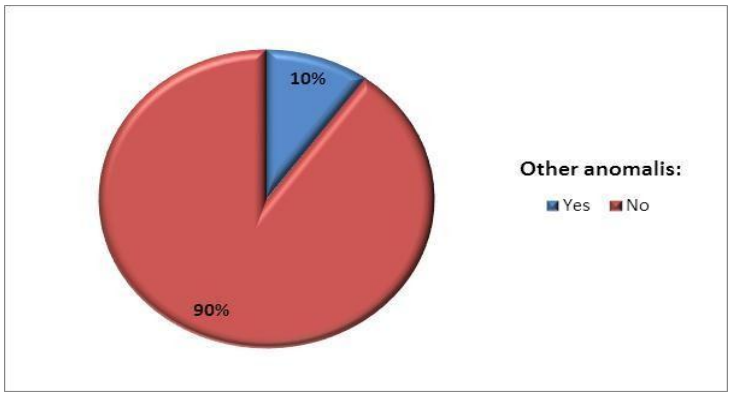


Figure (2): The distribution of other anomalies among DS patients



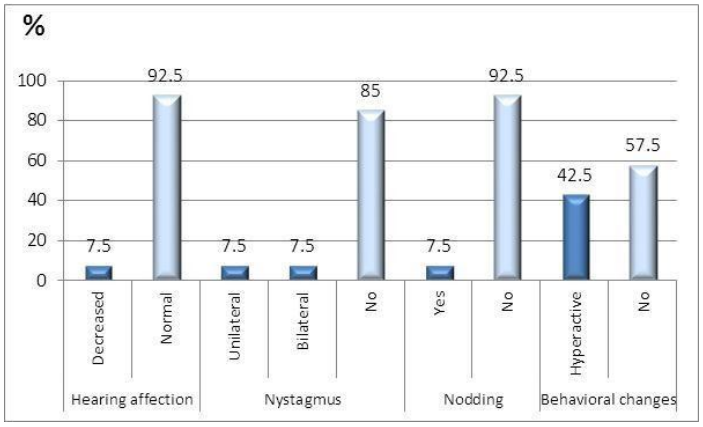
This table illustrates that 7.5% had decreased hearing acuity. ABR was done for 3 children, two of them showed bilateral moderate conductive hearing loss ,and one child had right side moderate, left side sever hearing loss. 15% had nystagmus (7.5% unilateral and 7.5% bilateral),

Fundus examination was done for 6 children, 3 children had normal fundus examination, one child showed papilledema, one child showed bilateral albenoid fundi with blunt foveal reflex,one child showed bilateral tigroid fundi with blunt foveal reflex.7.5% had head nodding . Hyperactivity was reported in 42.5% of cases.

Table (5): Neurological and behavioral manifestation of Downs's patients:

Variable	N	%
Hearing affection:		
Decreased	3	7.5
Normal	37	92.5
Nystagmus: Unilateral	3	7.5
Bilateral	3	7.5
No	34	85.0
Nodding:		
Yes	3	7.5
No	37	92.5
Behavioral changes:		
Hyperactive	17	42.5
No	23	57.5

Figure (3): Description of neurological and behavioral manifestation of Downs's patients

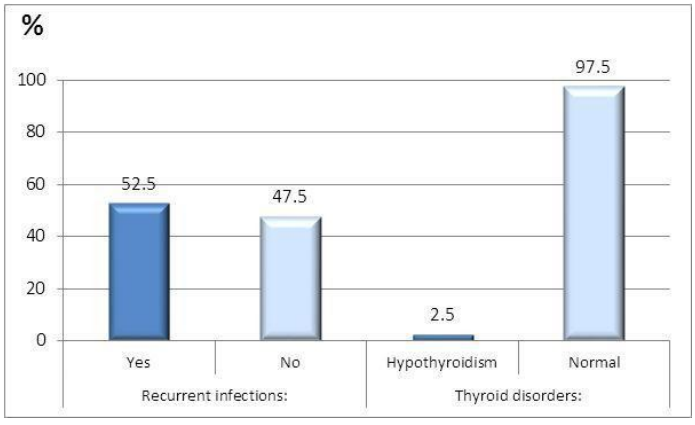


Large numbers of candidates (52.5%) showed history of repeated hospital admission. Recurrent infections in the form of chest infections (bronchiolitis and pneumonia) and gastroenteritis were reported. Hypothyroidism was reported in one case (2.5%). The proper treatment was described.

Table (6): Other associated manifestation:

Variable	N	%
Recurrent infections:		
Yes	21	52.5
No	19	47.5
Thyroid disorders:		
Hypothyroidism	1	2.5
Normal	39	97.5

Figure (4): Description of other associated manifestation



DISCUSSION

The aim of our study was to assess the neurodevelopmental outcome of children with Down syndrome.

Our study included 40 children with down syndrome, age of patients ranged from 1-96 months. Fourteen out of forty cases were females (35%) and 26 cases were males (65%).

The enrolled participants were subjected to full history taking, neurological examination, assessment of thyroid function, In selected cases ABR, fundus examination, and MRI study were done.

In our study, there is statistically significant difference between normal and Down percentile for weight. The study performed by (Anneren et al., 1990) in the Department of Genetics and Pathology assumed that the growth pattern in DS patients is characterized by an impaired growth velocity from birth until adolescence, especially during the age interval of 6 months to 3 years and during puberty.

In our study height & head circumference measurement showed significant statistical difference with significant p value <0.0001 between normal and down percentiles.

Our results were similar to a study was done in Netherland by (Hlma et al., 2012) which compared growth between children with Down syndrome and normal children from the general population.

The study showed that height and head circumference were smaller in children with Down syndrome resulting in shorter final stature and smaller head circumference than the general Dutch population.

Maternal age affects the chances of having a pregnancy with Down syndrome. Although the probability increases with maternal age, 70% of children with Down syndrome are born to women 35 years of age and younger, because younger people have more children (Morris et al., 2002).

Regarding maternal age, the mean age of mothers was (32.42±7.04) years ranged between (19 years and 44 years). Our results reported a high rate of DS births among young mother which is similar to the study by Morris et al., 2002. Another study by (Malini et al., 2006) in Mysore, South India, had revealed that 75% of DS children were born to young mothers, whose ages ranged from 18-29 years. However, Fisch et al., 2003 found that advanced maternal age significantly influences the incidence of Down syndrome.

Regarding cardiac anomalies, 50% of Down syndrome patients had cardiac problems, 22.5% had ASD which is the most common congenital heart disease followed by VSD (17.5%),ASD and VSD (2.5%), Fallot tetralogy (2.5%), Tricuspid regurgitation (2.5%), PFO (2.5%).

Our results, were similar to the study performed by Amet., 2016 showed that 40%-50% of newborns diagnosed with trisomy 21 have heart defects, with the most common heart defect AV canal defect (45%),other anomalies as VSD (35%), ASD (8%), Patent ductus arteriosus(7%), tetralogy of Fallot (4%) were also reported.

Another study by stoll et al., 2015, had Cardiac anomalies in44%, with the most common cardiac anomaly was atroventricular septal defect (30%), followed by ASD (25%), VSD (22%), patent ductus arteriosus (5%), coarctation of aorta (5%), and tetralogy of Fallot (3%).

In our study other congenital anomalies were detected in 4 patients (10%) in the form of umbilical hernia (2.5%), undescended testis (2.5%), imperforate anus (2.5%), megacolon (2.5%).

claude et al., 2015 reported that digestive system anomalies among the cases with DS recorded, duodenal atresia (67%), Hirschsprung disease (14%), and trachea-esophageal atresia (10%) were the most common.

In our study, 7.5% had decreased hearing acuity which were mainly conductive hearing loss, Raut et al., 2011 showed a higher percentage of hearing defect (34%), 85% were conductive.

The anatomical basis for the low tone is believed to be the result of microscopic changes in the development of the cerebellum (Guidi et al., 2011).

Nystagmus was reported in 15% of DS patients in this study. This was consistent with the study performed by Felius et al., 2014 that showed nystagmus in 3% to 33% of children with DS.

Nodding syndrome is characterized by a nodding behavior of the head in the form of (yes) or (no) movement. Cerebellum hypoplasia is responsible for muscle hypotonia and axial control (axial truncal muscle), and body balance, coordination, and speech disorders (Sveljo et al., 2014).

However, Melissa, 2011 reported that is accompanied by convulsions, staring spells, or other manifestations of seizures.

Head nodding was reported in 7.5% of cases in this study.

Hyperactivity was reported in 42.5% of the studied cases. This was also reported in a study by Ekstein et al., 2011 with 43.9% incidence of hyperactivity among studied cases with DS.

Large numbers of candidates (52.5%) showed history of repeated hospital admission. Recurrent infections in the form of chest infections (bronchiolitis and pneumonia) and gastroenteritis were reported, our results agree with Kusters et al., 2009, and Ram and Chinen., 2011.

In this study only one case (2.5%) had hypothyroidism, this result agrees with the study done by Olga et al., 2004 that reported an incidence of 1% of hypothyroidism in DS cases. Another study conducted by Coleman 1994 showed lower incidence (0.7%) of hypothyroidism in DS cases.

CONCLUSION

In conclusion, our data showed developmental delay in DS cases; all areas of development were affected (motor, self-help, communication, cognitive, and language skills). Presence of microcephaly affect most areas of development (motor, self-help, communication, and language skills). Neither the cytogenetic type, nor the consanguinity of the parents affects the developmental outcome. Hearing affection is considered in DS children; nystagmus and head nodding were observed in DS children, they showed high percentage (42.5%) of hyperactivity.

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