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A Review Article in:

The association between Down's syndrome and other health issues and diseases

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بسم الله الرحمن الرحيم

(قَالَ الَّذِي عِنْدَهُ عِلْمٌ مِنَ الْكِتَابِ أَنَا آتِيكَ بِهِ قَبْلَ أَنْ يَرْتَدَّ إِلَيْكَ طَرْفُكَ فَلَمَّا رَآهُ مُسْتَقِرًّا عِنْدَهُ قَالَ هَذَا مِنْ فَضْلِ رَبِّي لِيَبْلُوَنِي أَأَشْكُرُ أَمْ أَكْفُرُ وَمَنْ شَكَرَ فَإِنَّمَا يَشْكُرُ لِنَفْسِهِ وَمَنْ كَفَرَ فَإِنَّ رَبِّي غَنِيٌّ كَرِيمٌ)

صدق الله العلي العظيم

[النمل: 40]

الاهداء

إلى صاحب السيرة العطرة، والفكر المستنير

الذي كان له الفضل الأول في بلوغي التعليم العالي

(والدي الحبيب)، أطال الله في عمره

إلى من وضعتني على طريق الحياة، وجعلتني رابط الجأش،

وراعتني حتى صرت كبيرة

(أمي الغالية)، حفظها الله من كل سوء .

.إلى إخوتي؛ من كان لهم بالغ الأثر في كثير من العقبات والصعاب

إلى جميع أساتذتي الكرام؛ ممن لم يتوانوا في مد يد العون لي

اهدي لكم مشروعي البسيط ومن الله التوفيق

الشكر و التقدير

بسم الله الرحمن الرحيم، والحمد لله رب العالمين الذي وفقنا وأعاننا على إنهاء هذا البحث والخروج به بهذه الصورة المتكاملة، فبالأمس القريب بدأنا مسيرتنا التعليمية ونحن نتحسس الطريق برهبة وارتباك، فرأينا (الطب) هدفا ساميا وحبا وغاية تستحق السير لأجلها، وإن بحثنا يحمل في طياته طموح شباب يحلمون أن تكون أمتهم العربية كالشامة بين الأمم. وانطلاقًا من مبدأ أنه لا يشكر الله من لا يشكر الناس، فإنني اتوجه بالشكر الجزيل للأستاذ الدكتور (شكر محمود) الذي رافقني في مسيرتي لإنجاز هذا البحث وكان له بصمات واضحة من خلال توجيهاته وانتقاداته البناءة والدعم الأكاديمي.

كما اشكر عائلتي التي صبرت وتحملت معي ورفدتني بالكثير من الدعم على جميع الأصعدة، واشكر الأصدقاء والأحباب وكل من قدم لي الدعم العلمي أو المعنوي، وأخيرا نتوجه بشكر خاص للأستاذ (إسماعيل إبراهيم لطيف) عميد الكلية المحترم لمساهمته الفعالة في تسهيل المشروع راجيا من الله التوفيق والسداد.

Abstract

Down's syndrome is one of the most leading causes of intellectual disability and millions of these patients face various health issues including learning and memory defects**.** It's a congenital anomaly characterized by trisomy of the 21st pair of chromosomes. DS is the most frequent genetic cause of intellectual disability (ID), which is a main clinical feature of DS. Thus, most persons with DS have some degree of ID that affects learning and cognition. Its well known and scientifically proved that there is a strong relationship between down syndrome and a wide range of other congenital anomalies and health issues that include cardiac, respiratory, digestive and neurodevelopmental disorders. We tried in this review to cover the most common and serious issues associated with the syndrome.

Keywords: Down's syndrome, trisomy 21, intellectual disability

Introduction

Down syndrome is one of the most leading causes of intellectual disability and millions of these patients face various health issues including learning and memory defects (1). The incidence of trisomy is influenced by maternal age and differs in population (between 1 in 319 and 1 in 1000 live births). DS has high genetic complexity and phenotype variability. Trisomic fetuses are at elevated risk of miscarriages and DS people have increased incidence of developing several medical conditions . Recent advancement in medical treatment with social support has increased the life expectancy for DS population. In developed countries, the average life span for DS population is 55 years (2). The most common cause of having a DS babies is presence extra copy chromosome 21 resulting in trisomy. The other causes can be Robertsonian translocation and isochromosomal or ring chromosome. Ischromosome is a term used to describe a condition in which two long arms of chromosome separate together rather than the

long and short arm separating together during egg sperm development. Trisomy 21 (karyotype 47, XX, + 21 for females and 47, XY, + 21 for males) is caused by a failure of the chromosome 21 to separate during egg or sperm development. In Robertsonian translocation which occurs only in 2-4% of the cases, the long arm of the chromosome 21 is attached to another chromosome (generally chromosome 14) (3).

It is consistent in the literature that advanced maternal age (AMA) is a primary risk factor in DS births. Its a major cause of foetal death in

humans, about 50% of spontaneous foetal loss during pregnancy (before 15 weeks of gestation), are related to DS. DS is the most commonly diagnosed chromosomal abnormality in live-born infants and the most recognised congenital aneuploidy (presence of an erroneous number of chromosomes, e.g. 45 or 47) associated with delayed physical and mental development. DS is the most frequent genetic cause of intellectual disability (ID), which is a main clinical feature of DS. Thus, most persons with DS have some degree of ID that affects learning and cognition. Most students with DS receive special education, while some can benefit from inclusive classroom settings (4). There are many documented congenital anomalies and clinical manifestations associated with DS that range from simple to life threatening conditions. In this review, we will demonstrate the most common congenital anomalies and the manifestations that occur in or associated with Down syndrome population.

Literature review

A number of clinical conditions occur more frequently in adults with Down syndrome than in the rest of the adult population. Some conditions are associated with specific dysmorphic features, while others are assumed to be due to accelerated ageing processes. Anomalous prevalence figures are quoted for some (5). we will discuss the most common congenital anomalies and their related diseases.

A study done on 728 fetuses with DS showed that The most common types of associated anomalies were cardiac anomalies, (44% of all cases with DS), followed by digestive system anomalies, (6%), musculoskeletal system anomalies, cases (5%), urinary system anomalies, cases (4%) respiratory system anomalies, cases (2%), eye anomalies, cases (1%), central nervous system anomalies, cases (0.8%), oral clefts, cases (0.8%), genital system anomalies, cases (0.5%), and abdominal wall defects, cases (6). Approximately half of children with Down syndrome have congenital heart disease, which, unfortunately, can be missed on routine examination. In one study of 81 newborn infants with Down syndrome, only 53% of those with congenital heart disease were correctly identified by clinical examination alone, 44% by chest radiograph alone and 41% by electrocardiography alone. Ninety-four percent of the infants without congenital heart disease were positively identified by clinical examination, 98% by chest radiograph, and 100%by electrocardiography. Echocardiography should permit diagnosis of all congenital heart disease in children with Down syndrome (7). Improved management of congenital heart disease has contributed to an increase in life expectancy for patients with DS, from 30 years in 1973 to 60 years by 2002. Pulmonary-artery hypertension, with or without congenital heart

disease, occurs in 1.2 to 5.2% of persons with DS. Early repair of heart defects and surveillance for airway obstruction have been recommended to minimize the risks of heart failure and irreversible pulmonary vascular disease (8). The essential morphological hallmark of an AVSD is the presence of a common atrioventricular junction as compared to the separate right and left atrioventricular junction in the normal heart. Other morphological features include defects of the muscular and membranous atrioventricular septum and an ovoid shape of the common atrioventricular junction. There is disproportion of outlet and inlet dimensions of the left ventricle, with the former greater than the latter as compared to the normal heart where both dimensions are similar (9).

The most common non-cardiac anomalies include digestive system anomalies and limb malformations. Using a health records of the congenital malformations covering an area of France for the years 1979 to 1996 when 398 new cases of Down syndrome were identified, 6% were found to have intestinal atresias (10). Structural problems may affect the gastrointestinal tract from the mouth to the anus but many conditions will occur in Down syndrome with similar frequency to other children. However, oesophageal, duodenal, and small bowel atresia or stenosis, annular pancreas causing small bowel obstruction, imperforate anus and Hirschsprung disease may be more common than in the general population (11). Obstruction in the gastrointestinal tract may be detected before birth by imaging techniques and so allow for planned intervention early after birth. If diagnosis is not made pre-birth no bowel actions, vomiting and a distressed baby indicating abdominal pain will suggest bowel obstruction and the need for urgent surgical intervention. Imperforate anus either total or partial may also occur and require surgery. Hirschsprung disease affects

about 2% of those with Down syndrome and manifests as a distended abdomen, poor weight gain, vomiting and constipation. Short segment disease can be difficult to diagnose (12).

The association of DS with HD has often been reported to result in poorer outcomes with regard to postoperative complications such as anastomotic leakage, recurrent enterocolitis, temporary or permanent soiling, fecal incontinence, persistent constipation and mortality. On the other hand, it has been indicated that the postoperative results including the rates of enterocolitis and constipation are similar to those in patients with HD alone, suggesting that DS has only minimal influence on the overall outcome of patients with HD. Thus, the prognostic outcome after surgical treatment of HD in children with DS remains controversial (13). It is well-known from the literature that children with DS become frequently constipated, which is often attributed to hypotonia or hypothyroidism. However, a study recently presented many troublesome features in rectal suction biopsies of patients with DS and chronic constipation that may cause diagnostic difficulties in the work-up for HD. Thus, HD can be easily overlooked and may be more common than currently appreciated. Therefore, it is important that all cases with DS and severe constipation should be investigated for HD (14). Almost all of the conditions that effect the bones and joints of people with Down syndrome arise from the abnormal collagen found in Down syndrome. Collagen is the major protein that makes up ligaments, tendons, cartilage, bone and the support structure of the skin. One of the types of collagen (type VI) is encoded by a gene found on the 21st chromosome (15). The major condition associated with the spine in Down syndrome is Atlantoaxial instability, which is the looseness between the first and second vertebrae of the neck. Another condition associated with the spine in Down

syndrome is scoliosis, which is the curvature of the spine to the side. While it appears to be more common in people with DS, the exact incidence isn't known. In the era when almost all children with DS were institutionalized, scoliosis may have been seen in up to half of them as they became adolescents. Treatment of scoliosis remains the same as in other children, with bracing being the initial therapy, followed by surgical intervention if necessary (16). Five to eight percent of children with DS will develop abnormalities of the hip. The most common condition is dislocation of the hip, which is also called subluxation. In this condition, the head of the thigh bone (the femur) moves out of the socket formed by the pelvis (the acetabulum). This dislocation may or may not be associated with malformation of the acetabulum. Instability of the patella (kneecap) has been estimated to occur in close to 20 percent of people with DS. The majority of cases of instability present only as kneecaps that can be moved further to the outside than the normal kneecap. Flat foot**,** also called pes planus, is seen in the vast majority of people with DS. In mild cases, the heel is in a neutral position. In severe cases, the heel rotates so that the person is walking on the inside of the heel (17).

Thyroid dysfunction is the most typical endocrine abnormality in patients with Down syndrome, the established risk factors for which are old age and female sex. Hypothyroidism can be either congenital or acquired at any age after birth. the estimated lifetime prevalence rate of thyroid dysfunction in Down syndrome varied widely in different studies (between 3% and 54% in adult patients), owing to variations in population size, age, laboratory assays and definitions of thyroid dysfunction used (18). antithyroid autoantibodies were found in 13–34% of adults and older children with Down syndrome who acquired hypothyroidism, with a gradual increase in the concentration of autoantibodies after 8 years of age.

approximately half of children with Down syndrome may have an elevated tsH level with normal t3 and t4 levels, which suggest subclinical hypothyroidism. A delay in maturation of the hypothalamic–pituitary–thyroid axis has been hypothesized as the probable cause, as tsH responses to tsH-releasing hormone tests were more exaggerated in patients with Down syndrome than in controls. among individuals with Down syndrome, hyperthyroidism occurs much less frequently than hypothyroidism (19). Women are usually fertile, and guidance on contraception is necessary. Conversely, men with Down syndrome are usually sterile. Mentally retarded persons are generally at greater risk of being sexually exploited, and counselling on behaviour and boundary setting may help to prevent this (20). Hematologic abnormalities are common in patients with DS, manifested as transient abnormal myelopoiesis (formerly called transient myeloproliferative disorder) in infancy, iron deficiency in childhood, and an increased incidence of leukemia. Transient abnormal myelopoiesis, a form of myeloid preleukemia, occurs in up to 10% of neonates with DS and is due to mutations in *GATA1*. The disorder, which occurs predominantly in newborns and almost always before the age of 5 years, usually resolves spontaneously, but early detection and monitoring by pediatric hematologic specialists are recommended, since the risk of leukemia among patients with transient abnormal myelopoiesis is 20 to 30%. Leukemia independent of transient abnormal myelopoiesis develops in 2 to 3% of all patients with DS, particularly acute myeloid leukemia, which responds to current therapies, and acute lymphoblastic leukemia, which tends to have a poorer outcome in children who have DS than in those who do not (21-22). Autoimmune thyroid disease (AITD) is the most frequent autoimmune disorder coexisting with DS. Among two major clinical outcomes of AITD, Graves' disease and Hashimoto's thyroiditis

(HT), HT most often accompanies DS. Histologically, HT is characterized by lymphocytic infiltration of the thyroid. T cells and B cells account for about 60% and 30% of infiltrating lymphocytes, respectively. The T cell population is mostly represented by helper (CD4+) and cytotoxic (CD8+) cells (23). Type 1 Diabetes mellitus occurs in 1.4–10.6% of individuals with DS that is significantly higher than in general population (0.1%). Furthermore, age at diabetes onset in DS infants is earlier compared with non-trisomic children (i.e., 7–8 vs. 10–14 years). In addition, a portion of children with T1D diagnosed within the first 2 years of life is markedly higher among DS population (22%) compared to that in general population (7%). Due to the immune dysregulation, the early onset of T1D in DS patients could suggest for a very overt autoimmune pathology compared to non-DS T1D subjects. Alternatively, the β cell population in DS patients is more susceptible to destruction mediated by immune cells. Several studies observed a much higher prevalence of thyroid disorders in children with DS and T1D than that usually described in DS without diabetes (24).

DS patients have greatly increased risk of early onset Alzheimer Disease. After the age of 50, the risk of developing dementia increases in DS patients up to 70%. There are various genes reported to cause early onset AD. Some of the genes described in the current literature are APP (amyloid precursor protein), BACE2 (beta secretase 2), PICALM (Phosphatidylinositol binding clathrin assembly protein) and APOE (Apolipoprotein E) etc. APP is an integral membrane protein which is concentrated in synapse of neurons and trisomy of this protein is likely to make significant contribution to the increased frequency of dementia in DS individuals. The triplication of Hsa 21 along with APP in people without DS has been recently shown to be associated with early onset AD (25). Moyamoya disease is an uncommon vascular abnormality with an

increased incidence among patients with DS.It is due to stenosis of the supraclinoid portions of the internal carotid arteries. Children present with alternating hemiplegia or a fixed, unilateral, strokelike deficit, whereas adults more often have cerebral hemorrhage. Cerebral revascularization surgery has been performed in specialized centers (26).

The most common urinary anomalies in cases with DS with urinary anomalies are obstructive defects (27). The most common anomalies of the other organs include lung anomalies, eye anomalies such as cataracts, hydrocephaly, cleft palate, hypospadias and congenital diaphragmatic hernia (28).

Conclusion

Down's syndrome is a common congenital anomaly and associated with many serious other congenital anomalies and increased tendency for a lot of other diseases. Because its very common cause for intellectual and cognitive disability, the people with this syndrome need more attention and more specialized care centers to improve their cognitive abilities because they are at high risk of exploitation and abuse.

الخلاصة

متلازمة داون هي أحد الأسباب الرئيسية للإعاقة الذهنية ويواجه الملايين من هؤلاء المرضى مشاكل صحية مختلفة بما في ذلك عيوب التعلم والذاكرة. إنه شذوذ خلقي يتميز بتثلث الصبغي للزوج الحادي والعشرين من الكروموسومات . متلازمة داون هي السبب الجيني الأكثر شيوعًا للإعاقة الذهنية، وهي سمة سريرية رئيسية لهذه المتلازمة وبالتالي، فإن معظم الأشخاص الذين يعانون منها لديهم درجة معينة من الاعاقة التي تؤثر على التعلم والإدراك. من المعروف والمثبت علميًا أن هناك علاقة قوية بين متلازمة داون ومجموعة واسعة من التشوهات الخلقية والمشكلات الصحية الأخرى التي تشمل اضطرابات القلب والجهاز التنفسي والجهاز الهضمي والنمو العصبي. حاولنا في هذه المراجعة تغطية المشكلات الأكثر شيوعًا وخطورة المرتبطة بالمتلازمة.

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