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Review Article

Anemia and Other Hematologic Disorder in Children with Down Syndrome

Dahook Abdullah Abualsamh[1]*, Afaf Abdulali Alsubhi[2], Naima Abdulaziz Alkhulaiwi[3], Abdulrahman Mohammed Sibieh[4], Abdullah Seraj Almalki[4], Shahad Khaled Alrashed[4], Nadeer Zaki Albaik[5], Ahood Ahmad Alrashidi[6], May Hamoud Alharby[6], Basmah Mohammad Shorog[7], Khulood Zaki Alaidaroos[2] and Abdulaziz Abdullah Alalawi[2]

[1]Pediatric Consultant and Clinical Genetics, East Jeddah General Hospital, Jeddah, Saudi Arabia

[2]Maternity and Children's Hospital, Jeddah, Saudi Arabia

[3]Eskan Dammam Dispensary (Ministry of Health), Dammam, Saudi Arabia

[4]Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia

[5]Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

[6]Unaizah College of Medicine, Unaizah, Saudi Arabia

[7]King Khalid University, Abha, Saudi Arabia

***Corresponding Author:** Dahook Abdullah Abualsamh, Pediatric Consultant and Clinical Genetics, East Jeddah General Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: Down syndrome (DS) is considered the most common aneuploidy that affects humankind; the incidence of DS is 1 in 700 livebirth in the United State. Associations between DS and hematological conditions of all component of blood (red blood cells, white blood cells, and platelet) have been addressed repeatedly in medical literature and gaining more focus recently. These conditions manifest particularly during childhood.

Aim of Work: This is an overview of different aspects related to hematological abnormalities in children with DS, with some focus on anemia in these children.

Methodology: A comprehensive and systematic search was conducted regarding hematologic condition associated with Down syndrome including anemia. PubMed and Google Scholar search engine were the mainly used database.

Conclusion: The American Academy of Pediatrics (AAP) recommended the annual screening for iron deficiency anemia (IDA) in children with DS starting at 1 year of age until the age of 18. The most recent study showed a high prevalence of macrocytosis, a finding that supports the recommendation by AAP to add ferritin and C-reactive protein (CRP) concentration to Hb level in the annual screening in patient with Down syndrome. The use of IST to treat DS patients with anaplastic anemia is safe and may carry a favorable outcomes with full response achievement and negligible adverse event. Transient myeloproliferative disorder TMD manifest during the newborn period and early infancy. The condition is considered pre-leukemic and it is a challenge to diagnose. It has a pathogenetic role in the development of AML in children with Down syndrome

Keywords: *Down Syndrome (DS); Aneuploidy; Iron Deficiency Anemia (IDA); C-reactive Protein (CRP)*

IIntroduction

Down syndrome (DS) is considered the most common aneuploidy that affects humankind; the incidence of DS is 1 in 700 livebirth in the United State [1,2]. The syndrome manifests clinically by a wide range of abnormalities and comorbidities that affect different systems and organs including the cardiovascular, gastrointestinal, and musculoskeletal. Children with DS require a close care and long monitoring and follow up.

Associations between DS and hematological conditions of all component of blood (red blood cells, white blood cells, and platelet) have been addressed repeatedly in medical literature and gaining more focus recently. These conditions manifest particularly during childhood. For example, children with DS are at higher risk of leukemia 10 to 20 time compared with the general population [3]. The incidence of acute myeloid leukemia (AML) is significantly higher with approximately 150-fold increase. A transient myeloproliferative disorder (TMD) during the newborn period and early infancy is another condition affects these patients. Although the risk of Iron deficiency anemia is similar between children with and without DS, the higher prevalence of macrocytosis among children with DS renders the diagnosis by red blood cell indices more difficult [4-7]. Anaplastic anemia is considered a rare complication of DS in affected children [8-14].

In this review, we will discuss different aspects related to hematological abnormalities in children with DS, with some focus on anemia in these children.

Methods

A comprehensive and systematic search was conducted regarding hematologic condition associated with Down syndrome including anemia. PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com) were the mainly used database. All relevant available and accessible articles of all types were reviewed and included. Case reports and case series were used for rarely reported conditions. The terms used in search were: Down syndrome, trisomy 21, anemia, iron deficiency anemia and hematologic disorder.

Iron deficiency anemia in children with DS

The American Academy of Pediatrics (AAP) recommended the annual screening for iron deficiency anemia (IDA) in children with DS starting at 1 year of age until the age of 18. This was their first published guideline regarding the management of children with Down syndrome; it was published in 2011 [1]. The recommendation is based on the fact that irreversible cognitive impairment is associated with iron deficiency anemia and as children with Down syndrome are at higher risk for neurocognitive deficits. The recommended screening is achieved by annual check of hemoglobin level (Hb). Additionally, if the child has a positive history of inadequate nutrition, which increase the risk of iron deficiency, AAP recommended additional investigation as ferritin and C-reactive protein and/or reticulocyte hemoglobin concentration [1]. However, the evidenced was not strong enough and many researcher recommended a further study about the importance of this recommendation. For one example, some researcher has found that the prevalence of iron deficiency is similar in children with DS and other children without the syndrome, hence there is no benefits for additional screening. It is safe to say that data about IDA prevalence among children with DS is scarce [15]. One of studies that has been cited in the guideline compared iron intake between 10 children with DS and similar number of control; iron intake was lower in patients with DS, however, iron intake is not a specific indicator for iron deficiency anemia. In addition, inferences based on this study should be made with cautions due to a very small sample size [16]. Another studies with 114 children and adolescent with DS found iron deficiency in only 10% of patients and iron deficiency anemia in only 3%, a result that is similar to prevalence in pediatric population [6]. Another study conducted by Tenenbaum A, et al. has examined the prevalence of anemia in 149 patients with DS aged 0 to 20 years, they found that less than 10 percent of these patients had anemia and only half of these patient had a diagnostic iron [17].

To address this uncertainty, a recent study that was published in 2019 aimed to examine the prevalence of anemia in children aged between 1 and 18 years old, especially IDA [15]. The study was designed as a retrospective cohort with data of 200 participant being collected from the Medical University of South Carolina electronic record for patient between 2012 and 2016. The researchers included patient diagnosed with Dawn syndrome and aged 1 to 18 Down syndrome (DS), with a documented Hb value. The presence of additional hematologic condition was set as an exclusion criterion. The hemoglobin cut-off for age and sex suggested by World Health Organization was used to define anemia [18].

Among the 200 participants with DS, Anemia was found to affect 22.5%. In the study, 18 percent of children between 1 - 5 years with DS had anemia; this is much higher prevalence than correspondent general population without DS as reported by National Health and Nutrition Examination to be 3.2%. The most type of anemia was normocytic which represented more than two third of all anemia among participants. Similarly, the prevalence of anemia among children aged 5 - 11 years with DS in the study was higher than general population; 24.2 versus 2 percent respectively. Normally, there is no need for anemia screening in healthy males aged between 5 - 11 and 12 - 29 years old due relatively low risk, the prevalence in these male are about 2% and less than 1% for each age group respectively [19]. However, adolescent males with DS In this cohort study showed a very high prevalence similar to younger children. Anemia has been shown to affect one fourth of this age group. Thus, the authors support the need for annual screening for anemia until the age of 18 for both genders [19]. Despite the well-known association between iron deficiency and microcytic anemia, many research suggest that macrocytosis (increased mean corpuscular volume [MCV]) in anemic patients with DS, this make the detection of IDA challenging and may complicate the diagnosis. In one study [7], researchers estimated that macrocytosis present in slightly less than half of children with DS, whereas Dixon., *et al*. estimation was much lower (22%). In this study, the result was similar to Dixon et al results with estimated prevalence of macrocytosis to be 27.5%. This high prevalence of macrocytosis support the recommendation by AAP to add ferritin and C-reactive protein (CRP) concentration to Hb level in the annual screening in patient with Down syndrome, especially in the presence of malnutrition risk [2]. Ferritin is a more specific to estimate the status of iron stores, but it is also an acute phase reactant that can be falsely elevated in times of stress, inflammation, or infection. In cases with elevated ferritin due to acute reaction, IDA could be masked and difficulty detected, this is similar to the masking caused by macrocytosis to low MCV seen in IDA. Hence, to distinguish false elevation of ferritin, C reactive protein (also acute phase reactant) should be obtained. High level of CRP indicated that ferritin elevation is due reaction and thus render its value less representative of iron status. In that situations, further testing of ferritin should be done in the near future. This study has an important limitation, due to lack of health record regarding the status of iron, the prevalence of IDA is not precise. Hence, despite the diagnosis of anemia was accurate, the authors were unable to establish the cause of anemia. In addition, authors find that the diagnosis of anemia in the record was inconsistent with normal reference for age-sex group. This is a consistent barrier to physician documentation and identification of abnormal Hb values. In one study, the omission rate of secondary diagnoses was estimated to be as high as 40 percent [20]. Hence, the author stated that they were not sure if physicians have addressed the presence of anemia in all patient with DS, thus the prevalence could be even higher. In addition, this was a single center study and hence the generalization of finding is not warranted.

Anaplastic anemia in children with DS

Among many predisposition for hematologic conditions, Down syndrome (DS) carries a risk for developing an idiopathic acquired aplastic anemia (AA). This complication is very rare with only 9 cases being reported prior to 2016 [8-14]. A recent case series including three cases was reported by Kyogo Suzuki., *et al*. in 2016 [21]. The researchers reported a case of two males and 1 female with DS that show idiopathic anaplastic anemia and studied the efficacy of immunosuppressive therapy (IST) for the first time in the literature.

The first patient was a two-year-old child. The patients had mild pulmonary hypertension mostly due to atrial septal defect. The child presented with fever. Blood test yielded marked pancytopenia and was diagnosed with severe form of anaplastic anemia after fulfilling the criteria. Further investigation by bone marrow aspiration revealed extreme hypocellularity without blast proliferation or

dysplastic features. The physicians started with two courses of high dose of steroid therapy. After about three months patient was given immunosuppressive therapy that constitutes of horse-derived antithymocyte globulin (ATG) and cyclosporine A (CSA). There was no apparent response after 3 and 6 months of therapy, however, patient start to show a complete recovery after 10 months. After 28 months patient developed immune thrombocytopenia which responded adequately to prednisolone. During continuous follow-up until the age of 17 years, patient did not show any other complication and blood cell counts were at normal level.

The second patient was an 8 year-old girl with a history of anal atresia and hyperthyroidism. The girl presented with bleeding tendency and blood test reveal pancytopenia with particularly prominent neutropenia. Patient was diagnosed with severe form of anaplastic anemia that was confirmed by bone marrow aspiration with hypocellularity. IST was started after 39 days of presentation and comprised ATG and CSA and granulocyte-colony stimulating factor. Similar to first case, there was no adequate response at 3 and 6 months follow-up. A partial response started to appear after 11 months of therapy initiation. Although sufficient hematopoietic recovery was not achieved at 3 and 6 months as observed in Case 1, a partial response occurred 11 months after IST. After 52 months follow-up, patient showed a good response with normal blood cell count despite a mild form of neutropenia.

The third case was about an 8-year-old boy with ventricular septal defect and patent ductus arteriosus. The child did not have any symptoms and was discovered incidentally by showing pancytopenia on Complete blood count (CBC). Additional investigation by bone marrow examination showed hypocellularity without blast proliferation. The diagnoses was established as anaplastic anemia. Patient was managed initially with oral CSA combined with danazol with no response. After that, bleeding tendency started to appear gradually and the patient needed periodic platelet transfusion. After 9 months, patient managed to receive IST with rabbit-derived ATG and CSA. Patient showed transient recovery. Eventually, IST did not lead to further responses and the patient needed bone marrow transplantation (BMT) after 12 months of IST.

This was the first study to examine the efficacy of IST in DS patient complicated with severe anaplastic anemia. One out of three patient did not respond to IST and the other two showed a complete recovery after one year of therapy that remained the same at the final follow-up. It is worth to mention that there was no obvious short-term response in the first 6 months of therapy initiation. In the third patient where IST did not show any efficacy, there was a delay in IST initiation that may explain the lack of response [22,23].

Allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling donor is the first-line and the definite therapy for severe anaplastic anemia. An alternative donor especially HLA-matched unrelated donor is the best option in case of no respond to IST. However, the evidence regarding allogeneic HSCT for Down syndrome patient is limited and the few published studies reported inferior outcomes compared to children without DS, in addition to reported mortality rate related to transplant complication [9,24]. In the recently published case series, the third patients also suffered various complications. Although some researchers suggest that DS patient may show a drug sensitivities different than general population [25,26]. The recent study of 3 patient did not report any unwanted effects of IST. The authors concluded that the use of IST to treat DS patients with anaplastic anemia is safe and may carry a favorable outcomes with full response achievement and negligible adverse event [21].

Transient myeloproliferative disorder

In addition to anemia, children with DS are prone to other hematologic abnormalities and diseases. Transient myeloproliferative disorder TMD (or transient leukemia) manifest in these patient during the newborn period and early infancy. The condition is considered pre-leukemic and it is a challenge to diagnose. It has a pathogenetic role in the development of AML in children with Down syndrome.

The disease is common among DS children, the reports have estimated the prevalence to range between 10 to 30 percent of children with DS [27-29]. When the screening is conducted through morphology of peripheral blood smear for the presence of blasts in suspected cases, TMD has been reported in approximately 10 percent of infants with DS [30]. Since peripheral blood smear may not be obtained

and examined microscopically on regular basis [31], the actual incidence is likely to be higher. This is evidenced by one prospective study that identified circulating blasts in 98 percent of neonates with DS [32]. When genetic sequencing is performed to detect somatic GATA1 mutations in peripheral blood cells [33], overt or clinically silent TMD was found in 29 percent of newborns with DS [32].

The basic molecular pathogenesis of Transient myeloproliferative disorder is a complex process with many steps that is not fully understood. There is a transient presence of blasts of megakaryocytic lineage in the peripheral blood of infants with trisomy 21. Transient myeloproliferative disorder starts to appear during fetal development and early hematopoiesis [31,34]. In the setting of trisomy 21, megakaryocyte-erythroid progenitors (MEPs) are expanded during hematopoiesis in the fetal liver [27,35,36]. A Somatic mutation of the gene coding for the hematopoietic transcription factor amino-terminally truncated GATA1 protein (GATA-1) is believed to be acquired for TMD development [36-40]. GATA1 mutations result in the expression of GATA1 protein. The functional consequence is impaired and uncontrolled megakaryocytic differentiation and proliferation [33]. The number of TMD blasts is found to be higher in the peripheral blood than in the bone marrow, this could be explained by the origin of TMD in tissues of fetal hematopoiesis as the liver [29].

Most cases (about 80%) of Transient myeloproliferative disorder resolves within the first three months of life. However, about 20 percent of apparent recovery is followed by the onset of acute myeloid leukemia (AML), typically within the first four years of life.

Conclusion

Down syndrome (DS) is considered the most common aneuploidy that affects humankind; the incidence of DS is 1 in 700 livebirth in the United State. Associations between DS and hematological conditions of all component of blood (red blood cells, white blood cells, and platelet) have been addressed repeatedly in medical literature and gaining more focus recently. These conditions manifest particularly during childhood. The American Academy of Pediatrics (AAP) recommended the annual screening for iron deficiency anemia (IDA) in children with DS starting at 1 year of age until the age of 18. The most recent study showed a high prevalence of macrocytosis, a finding that supports the recommendation by AAP to add ferritin and C-reactive protein (CRP) concentration to Hb level in the annual screening in patient with Down syndrome. The use of IST to treat DS patients with anaplastic anemia is safe and may carry a favorable outcomes with full response achievement and negligible adverse event. Transient myeloproliferative disorder TMD manifest during the newborn period and early infancy. The condition is considered pre-leukemic and it is a challenge to diagnose. It has a pathogenetic role in the development of AML in children with Down syndrome.

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