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Genotype and Phenotype of Adenosine Deaminase 2 Deficiency: The Experience From Saudi Arabia

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Abstract

Purpose

DADA2 is a rare and potentially fatal systemic autoinflammatory disease characterized by reduced or absence of ADA2 enzyme activity resulting from mutations in the ADA2 gene. Symptoms of DADA2 are variable and include vasculitis, immune dysregulation, and cytopenia. Scattered Saudi cases of DADA2 have been reported. We describe clinical, molecular, and outcome characterization of Saudi cases focused on phenotypic variability of DADA2.

Methods

To summarize the clinical features of Saudi patients with DADA2, we conducted a retrospective observational study in the seven major tertiary medical centers. Analysis of clinical characteristics, diagnostic findings, and treatment outcomes was obtained.

Results

We identified 21 individuals with DADA2 from 14 families. At the time of the study, the patient's age was between 4 and 26 years (median age of 11.3 years). 20 patients presented during childhood. Homozygous c1447-1451del of ADA2 was the most frequently observed mutation in 38%, followed by c882-2A: G in 29%. Absent ADA2 activity was identified in all tested patients with homozygous mutations. Phenotypic manifestations included vasculopathy (stroke or cutaneous lesion) in 48%, cytopenia in 95%, autoinflammatory features such as intermittent fever, transaminases, and hepatosplenomegaly, and or immunodeficiency in 71% of the patients. 4 patients presented with Hodgkin lymphoma and one patient presented with clinical features mimic transverse myelitis, adding to the clinical spectrum of DADA2. Anti-tumor necrosis factor (anti-TNF) is the main treatment. However, regular blood transfusion, splenectomy, cyclosporine, and hematopoietic stem cell transplant (HSCT) were initiated in other patients because of anti-TNF failure. Morality was reported in 3 patients due to fulminant hepatitis and septic multi-organ failure.

Conclusion

Our cohort expands the variability of molecular and clinical characteristics of DADA2. Hematological phenotype predominates in the patients. Consensus diagnostic criteria are required to facilitate early diagnosis and initiation of prompt therapy. Evaluation of the rare disease complications such as cancer needs large prospective studies or disease registries

Introduction

The deficiency of adenosine deaminase 2 (DADA2), initially described by two separate groups in 2014, is a systemic autoinflammatory disorder characterized by varying degrees of three major manifestations: vasculitis and dysregulation of immune function, and hematological abnormalities. Biallelic deleterious

mutations cause molecular pathogenesis of DADA2 in adenosine deaminase 2 (*ADA2*) on chromosome 22q11 [1, 2, 3]. The disease is a rare autosomal recessive disorder with an estimated prevalence of 4:100000 [4]. However, DADA2 is higher in communities with a greater level of consanguinity and in populations with reported founder mutations (the Middle East and northern Europe) [5, 6, 7]. In addition to catalyzing the conversion of adenosine to inosine, ADA2 acts as an outside extracellular growth factor for the integrity of endothelial cells and in the development of specific myeloid cells; however, the entire pathophysiology of DADA2 is not well defined [8].

Patients with DADA2 have wide phenotypic variability in the age of onset, frequency, and severity of clinical manifestations observed among both affected families and siblings [9]. However, it is a childhood disease. Age of onset is most often 5 to 7 years, with 25% and 77% of patients present before 1 year and 10 years of age, respectively [10]. The disease is a common cause of early-onset vasculitis in children [11]. Systemic autoinflammatory manifestations often accompany cutaneous vasculitis and ischemic or hemorrhagic stroke [12]. However, several reports on patients with DADA2 described the predominance of hematological and immunological manifestations, including hypogammaglobinemia, lymphopenia, neutropenia, thrombocytopenia, pure red cell aplasia (PRCA), and bone marrow failure [13–15]. Vasculitis phenotype appears to be linked to missense mutations and residual ADA2 protein function, while hematologic phenotype is found in individuals with insertion/deletions, nonsense, or missense mutations and loss of the enzyme ADA2 activity [16]. The association of DADA2 with lymphoproliferation is well known; splenomegaly and lymphadenopathies have been described in 30% and 10% of cases, respectively. Autoimmune lymphoproliferative syndrome (ALPS), multicentric Castleman disease, T-cell large granular lymphocyte leukemia (T-LGL) like disease, and recent association with Hodgkin lymphoma (HL) have all been reported in patients with DADA2 [17–22].

Diagnosis of DADA2 is established in a patient with suspected clinical and laboratory findings by identifying biallelic pathogenic variants of *ADA2* and/or absent or low (< 5% of normal) plasma ADA2 activity [3, 10]. Currently, anti-tumor necrosis factor (anti-TNF) therapy (etanercept, infliximab, adalimumab) is the standard of care to treat and prevent auto-inflammatory and vasculitis manifestations [23]. Nevertheless, TNF inhibition is less effective in treating bone marrow failure [16]. In several reported studies, hematopoietic stem cell transplant (HSCT) has cured vascular, hematological, and immunological manifestations of DADA2 [24, 25].

Reports from Saudi Arabia on individuals diagnosed with DADA2 are scattered. It remains unclear whether Saudi patients with DADA2 play a role in expanding the genotype and phenotype variability of DADA2. Therefore, this study was undertaken to describe Saudi features of DADA2, including clinical characteristics, genotype, and disease outcome.

Methods

We conducted a retrospective observational study in the seven major tertiary medical centers. The primary investigator invited hematologists, rheumatologists, and immunologists in the study centers,

including authors of published case reports of DADA2, to participate in the current study. After the appropriate informed consent from patients or their parents and approval by the Ethics Committee of Prince Sultan Military Medical Military City (study number 01/SC1-FA-5/2/21), patients' medical data analysis was obtained, including clinical characteristics, diagnostic findings, and treatment outcomes. The criteria for patient inclusion in the study was molecular genetic diagnosis of DADA2 and/or plasma ADA2 activity level in the diagnostic range (absent or low < 5% of normal plasma level). Molecular testing was done at Centogene genetic laboratory center using whole-exome sequencing. The results were confirmed by Sanger sequencing. ADA2 enzyme activity was measured in extracts of dried plasma spots on filter paper [26]. Patients with suspected clinical findings but incomplete data for genetic testing or ADA2 enzyme activity were excluded from the study.

Results

Demographic data

We present 21 patients with genetically confirmed *ADA2* mutations in 14 families from 7 medical centers in Saudi Arabia, including updates of previously reported six patients (A1, A2, D, F, K, and L). Demographic features, clinical characteristics, genetic study, therapeutic response, and outcome for all patients are summarized in Table 1. The study group was Saudis except for one patient from Sudan (J) who lives in Saudi Arabia. Four families had more than one patient (family A: 2 patients, family B: 5 patients, family E: 2 patients, and family N: 2 patients). Consanguinity was noticed in more than 90% of patients. The male-female ratio was 1:1.6. At the time of the study, the patient's age was between 4 and 26 years, with a median age of 11.3 years old.

Age at presentation was between neonate and 24 years, with 48% (10 patients) had presented before 2 years old and 86% (18 patients) before 5 years old. The median time between initial presentation and diagnosis was 3.9 (0.2-11 years). A few patients had a particular time at presentation and diagnosis. Twins B1 and B2 presented at birth with inguinal lymphadenopathy that progressed to generalized lymphadenopathy and splenomegaly over a few months. E2 and M presented with anemia and hepatosplenomegaly before the description of DADA2 in 2014. Both patients were diagnosed by molecular genetic testing after death. Four patients (A1, A2, B3, and L) presented with HL. Patient B3 is the symptomatic carrier with a single deleterious *ADA2* variant with an intermediate level of *ADA2* enzymatic activity.

The initial presentation was autoinflammatory features (intermittent fever, transaminases, and hepatosplenomegaly) in 71% of the patients (15/21). Intermittent fever was present in 7 patients (33%). Ten patients (48%) had hepatosplenomegaly, while twins B1 and B2 had splenomegaly without liver enlargement. Five patients suffered from cutaneous lesions, including PAN, cutaneous ulcer, and digital necrosis. Of the 21 patients, 5 patients (24%) showed aphthous ulcers. Musculoskeletal features (myalgia or arthralgia) were present in 4 patients (19%). Among the 15 tested patients for brain MRI, stroke was present in 6 patients, 40% (6 ischemic and 1 hemorrhagic) figure 1. I suffered from lower limb weakness

that resembled transverse myelitis. Lymphadenopathy was reported in 6 patients (29%). Lymphopenia was noted in 13 patients (62%). Recurrent infection and hypogammaglobinemia were observed in 9 (43%) and 7 (35%) patients, respectively. Recurrent infections included cytomegalovirus (CMV) infection (viremia and retinitis), BCG disease, or BCGitis (purulent regional lymphadenitis after bacilli Calmette-Guerin vaccine), typhlitis, fistula and abscess of bowel and urogenital tract, furunculosis, lower chest infection, and septic shock. Additionally, observed organisms are each in one patient, including methicillin-resistant staph aureus (MRSA), pseudomonas, candida, and mycobacterium riyadhense. Growth retardation impacted 6 patients, including two patients (twins B1 and B2) who required growth hormone treatment.

Laboratory testing

Hematological abnormalities were observed in 20 patients (95%); neutropenia in 76%, pancytopenia in 33%, and anemia was similar to thrombocytopenia in 43%. Immune hemolytic anemia was noted in two patients. Erythrocyte sedimentation rate (ESR) was elevated in 6 patients, 3 of them in combination with elevated C-reactive protein (CRP). All 13 tested patients were negative for antineutrophilic cytoplasmic antibodies (ANCA). Transaminases were noted in 2 patients and proteinuria in one patient.

ADA2 activity and mutation

Plasma ADA2 activity was performed in 6 patients while molecular genetic testing confirmed the diagnosis of DADA2 in all patients. ADA2 activity was undetectable in four patients (A1.A1, B1, and B2), reduced in one patient (F), and lower normal in the patient with the carrier status (B3) Table1. We identified 7 different mutations. 19 patients were homozygous, one patient was compound heterozygous (C), and one (B3) was heterozygous. Homozygous c1447-1451del was the most frequently observed mutation in 8/21 patients (38%), and c882-2A: G was reported (in 6 patients) as the second common mutation.

Treatment and outcome

Initial therapy in our cohort was variable and included corticosteroids (10 patients), IVIG (7 patients), anti-TNF therapy (5 patients), G-CSF (4 patients), MMF (1 patient), rituximab (1 patient), and eltrombopag (1 patient). Three patients responded to initial treatment with anti-TNF, while the other two had to change therapy because of treatment failure. Current treatment included anti-TNF therapy (9 patients), G-CSF (3 patients), chronic blood transfusion (3 patients), cyclosporine (2 patients), IVIG (2 patients), and post-HSCT (1 patient). The clinical course of patient F was dominated by bone marrow failure and lymphoproliferation, which prompted HSCT from matched sibling donor who was normal on genetic testing for *ADA2.* [18] Targeted busulfan, fludarabine, and ATG was utilized as conditioning regimen. F tolerated HSCT well and was cured. Anemia mimicked PRCA in 29% (6 patients) of the cohort. Two patients (E2 and M) died because of fulminant hepatitis and septic MOF. H died because of septic shock. Three patients (k, N1, and N2) remained on chronic blood transfusion support, and one patient, A1, was

refractory to anti-TNF treatment but responded to splenectomy, cyclosporine, and monthly IVIG treatment Table1.

Discussion

We report here the Saudi result from a multi-center study of a cohort of 21 patients with confirmed DADA2, including the update of previously reported 6 cases [18, 22, 27, 28]. Disease onset in our cohort remained in childhood, similar to the literature report. The mean age at presentation was 3.6 years, and 95% were less than 10 years. About 30% of our cohort presented before the first year of life. Indeed, the presentation of 4 patients (B1, B2, E2, J, and M) at birth or soon after birth emphasize the importance of considering DADA2 in patients with suspected clinical manifestation at such age. Only one patient (B4) presented with cutaneous vasculitis and cytopenia in adulthood. Presentation later in adulthood or asymptomatic individuals with DADA2 are well described in several reports. Indeed, patients with a predominance of the vascular phenotype are increasingly diagnosed by adult care providers [21, 29–31]. Molecular genetic testing and ADA2 enzyme levels are the diagnostic tools for DADA2. However, measurement of ADA2 enzyme activity may not be available in clinical laboratories, which made molecular genetic testing widely used [3, 10]. Diagnostic delays of DADA2 patients are observed in our cases. Time to diagnosis was prolonged with a mean of 3.9 years and may reach 11 years. Variability of phenotype, the rarity of the disease, limited availability of ADA2 enzyme testing, and poor awareness of DADA2 among physicians may impede consideration of this disease in the differential diagnosis with subsequent diagnostic delay. The establishment of a consensus diagnostic criteria for DADA2 may minimize such delay [32, 33]. Furthermore, the diagnosis of two (E2 and M) of our cohort after death highlight the need to enquire about unexplained deaths in the family on evaluating a patient with suspected DADA2.

The study sample is much less in number; however, in comparison to the analysis of 160 patients with DADA2 reported from the USA, Europe, and Turkey in one article [10], our cases are different in some clinical manifestations, including the frequency of phenotypes and genetic mutations (Fig. 2). The hematological and immunological manifestations predominate our cohort. Skin vasculitis and autoinflammatory features such as fever are less frequent at home than abroad. However, stroke is consistent in both cohorts. The frequency of cytopenias and impaired innate immunity are higher in our cohort. Tested ADA2 enzyme levels in our patients showed activity loss that coincides with their predominance of hematological phenotype [16].

Other rare clinical features, including growth retardation and complicated gastrointestinal ischemia, were reported in our cohort too. However, growth retardation, rigorously described in recent DADA reports, is found to impact a significant number (30%) of our patients [34]. Vasculitis manifestations of the gastrointestinal system generally include abdominal pain and, on rare occasions, intestinal necrosis with subsequent bowel perforation [12] Patient I, who presented with vasculitis phenotype, was noticed to have lower limb weakness that mimics transverse myelitis, which has not been previously described in children with DADA2.

Distinct *ADA2* mutations are reported in different ethnicities. For instance, the most frequent mutations in affected individuals are p.Gly47Arg in Turkish and Georgian-Jewish ancestry and p.Arg169Gln in Northern Europe population [5, 6, 7] *ADA2* c1447-1451del and c882-2A: G are the most common identified mutations in 38% and 29% of our patients, respectively. G47R mutation was detected in one patient (I) with the predominance of vasculitis phenotype. One patient carried the R169Q mutation. Over half of DADA2 patients in the literature have homozygous ADA2 mutations [35]. While all our cohort but one are homozygous for ADA2 mutations and more than half of the patients had a family history of the disease (Table 1). The rate of consanguinity in the Saudi population was estimated in a large genetic study to be at 57%. [36] Thus, it is prudent to clarify the genetic status of relatives at risk and commence therapy accordingly to prevent complications.

Upon reviewing the ACMG variant classification 2015 and Varsome database, c.1447_1451del variant results in an amino acid change leading to an outframe deletion as delineated p. (Ser483Profs*5) and subsequently deleterious impact on the final protein function as well as structure which became evident by the complete enzymatic deficiency [37]. Thus, this variant is classified as pathogenic. The other variant, c.882-2A > G, disrupts the splicing of the final protein. Furthermore, the undetectable enzyme level has placed c.882-2A > G in the pathogenic classification. C has compound heterozygous variants, c.389_407del p.(Tyr130Serfs*48) and c.505C > T p.(Arg169Trp), the first variant yields a significant deletion of 19 nucleotides and outframe shift deletion resulting in a stop codon; this variant was not seen in any database including OMIM and to be classified as a likely pathogenic based on ACMG guidelines 2015. The latter one, c.505C > T p.(Arg169Trp), has been a classified variant of unknown significance, yet it has pathogenicity features. This sequence change replaces arginine with tryptophan at codon 169 of the ADA2 protein (p.Arg169Trp). The arginine residue is highly conserved, and there is a moderate physicochemical difference between arginine and tryptophan. This variant is not present in population databases. Additionally, c.505C > T disrupts the p.Arg169 amino acid residue in ADA2. Other variants (s) that disrupt this residue have been pathogenic (PMID: 24552285, 26867732, 24552284, and 25888558). These suggest that this residue is clinically significant and that variants that disrupt this residue are likely to be disease-causing Table 2.

The diverse clinical manifestation of DADA2 is observed in our patients, even among the same family. For instance, A1, despite multiple therapeutic trials, continues to suffer from severe disease due to transfusion-dependent cytopenias and recurrent infections, while his brother (A2) remained asymptomatic with no treatment. Springer et al. reported an adult patient with DADA2 who suffered from HL during early childhood [17]. Our previous studies reported three cases (A1, A2, and L) of HL associated with DADA2 with a novel deleterious mutation in *the ADA2* gene [22, 28]. In the current study, we report an additional case of HL in (B3) the symptomatic carrier (single deleterious pathogenic ADA2 variant: c.882-2A: G). The observed association between HL and DADA2 in B3 adds additional cases in the literature and strengthens our team's reported data. B3 shows that in addition to the association between HL and DADA2, carriers of DADA2 could clinically and complication-wise behave as homozygous patients [11, 32]. This association between DADA2 and HL should alert the hemato-oncologist to the possibility of DADA2 as an underlying diagnosis in childhood HL, particularly in FHL and in the HL patient with an

aberrant course and additional symptoms/signs as it is potentially essential both for genetic counseling as well as for optimal treatment.
The literature's most frequent clinical manifestations of DADA2 are related to small and medium arterial vasculopathy. Vasculitis most characteristically involves the central nervous system. Vasculopathy of the CNS manifests as early-onset (i.e., age less than 10 years) lacunar and/ or hemorrhagic strokes in one-third of DADA2 patients [3, 10]. Ischemic strokes are often small and deep in the brain stem, basal ganglia, thalamus, and internal capsule. Consequently, such strokes might not be evident in brain MRI or often manifest as silent strokes. Most individuals with abnormal brain MRI in our series had a silent ischemic stroke. Even without overt neurological manifestations, early detection of stroke by MRI brain and initiation of anti-TNF is recommended to prevent the accumulation of recurrent small infarcts that can lead to severe neurological impairment such as cranial nerve palsies, dysarthria, ataxia, and cognitive dysfunction [17].

Anti-TNF is the main current therapy in our cohort. TNF-inhibition in our cases is effective in preventing additional strokes [23]. However, for patients with a severe hematological phenotype including bone marrow failure and PRCA, TNF-inhibitor failed to reverse the hematological manifestations indicating the need for HSCT. Indeed, the most common reported indication for HSCT in DADA2 patients is cytopenia and or immunodeficiency, not responding to anti-TNF treatment [24, 25]. A1 suffered from corticosteroid-dependent PRCA and anti-TNF refractory cytopenia that responded to splenectomy, cyclosporine, and monthly IVIG. The role of splenectomy in treating cytopenia in patients with DADA2 is unclear; however, to date, there is insufficient data to establish risk-versus-benefit comparison definitively [38].

Conclusion

DADA2 is a rare multi-systemic auto-inflammatory disorder that results in multiple clinical manifestations, including vasculopathy, immunological dysfunction, and hematological abnormalities. Our cohort showed the predominance of hematological phenotype and homozygous *ADA2* c1447-1451del and c882-2A: G mutations. The disease is underdiagnosed. Awareness among physicians needs improvement. The disease should be considered in the differential diagnosis of multiple conditions: vasculitis, stroke, cytopenia, and immunodeficiency. Hence, the establishment of a consensus diagnostic criteria might be helpful. Our case series expand the genotype and phenotypic variability of DADA2. Large prospective studies or disease registries are needed to evaluate cancer risk in patients with DADA2.

Declarations

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Authorship Contribution

FA and TA collected, analyzed, and wrote the manuscript. FA, TA, and AR interpreted data. AR, ME AS, SM, SMA, AA, DS, WB, NB, EH, AH, SR, FB, HF, TA, MQ, MH, HD, HJ, ST, and ASU provided clinical information from patients medical records and edited the manuscript. GY collected the laboratory data and edited the manuscript. AH collected the radiological data and edited the manuscript. All authors approved the submitted manuscript

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Conflicts of interest/Competing interests

The authors declare that they have no conflicts of interest.

Availability of data and material

All data generated or analyzed during this study are included in this manuscript

Ethics approval

The ethics committees of Prince Sultan Medical Military City approved the study (01/SC1-FA-5/2/21)

Consent to participate

Written informed consent was obtained from the parents or patients following a full explanation of the nature of the study

Consent for publication

Written consent obtained

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Tables

Table 1, 2 is available in the Supplemental Files section.

Figures

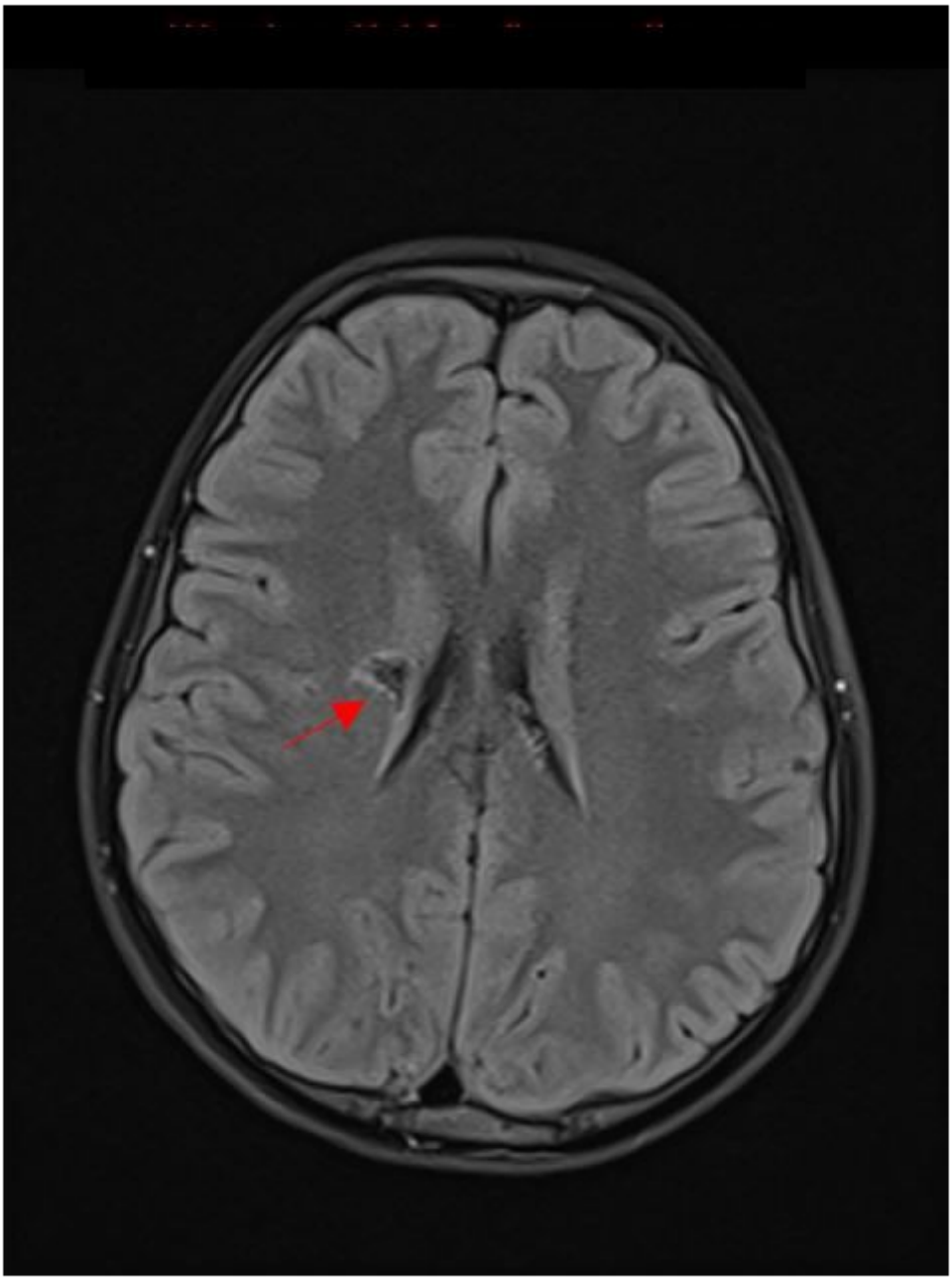

Figure 1

Old ischemic stroke (red arrow) seen at the right basal ganglia on an axial view of cerebral magnetic resonance image (MRI) of patient B5.

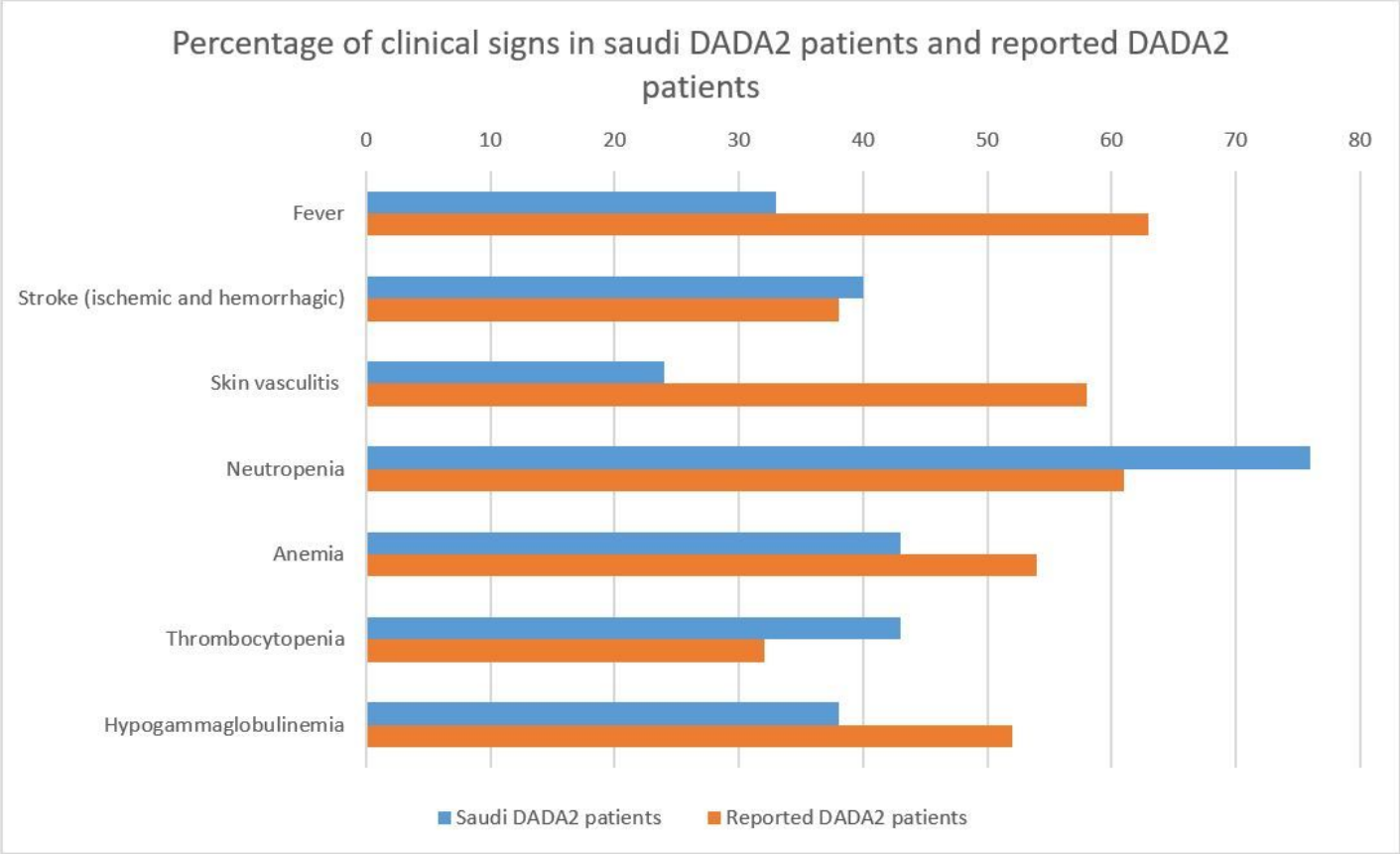

Figure 2

Bar graph illustrating the frequency of the common clinical signs seen in Saudi patients (21) with DADA2 versus reported (160) DADA2 patients. [10]

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.jpg