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Review Article

Overview of ACKR1/DARC-Associated Neutropenia (ADAN) and the Potential Clinical Implications of This Condition in Clinical Practice

H Al-Qayyim[1]*, L Balakrishnan[1]*, P Sriskandarajah[1]

[1]Department of Haematology, Guy's Hospital, London, SE1 9RT, United Kingdom.

*These authors contributed equally to this work.

***Corresponding Author:** Priya Sriskandarajah, Department of Haematology, Guy's Hospital, London, SE1 9RT, United Kingdom. E-mail: priya.sriskandarajah@nhs.net

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Abstract

Neutropenia is one of the most common referrals to the general haematology clinic, and is particularly prevalent in patients of African background. This is unsurprising as these patients often have ACKR1/DARC-associated neutropenia (ADAN), previously known as Benign Ethnic Neutropenia (BEN). To date, ADAN has not been known to have an impact on underlying bone marrow function and is generally monitored. However, recent studies do suggest that ADAN could be implicated in non-haematological conditions. Furthermore, ADAN has been shown to impact delivery of treatment for other disease areas including psychiatric disorders and cancers. Our review article focuses on the pathophysiology of ADAN and importantly on its potential influence on other disorders, both directly and indirectly. Finally, we discuss how research may be warranted to better our understanding of this condition.

Keywords: *Neutropenia; Duffy; Inflammation; Malignancy*

Introduction

Neutropenia is a common reason to refer patients to secondary care as it is associated with increasing risk of infection/ sepsis as Absolute Neutrophil Count (ANC) decreases. The definition of neutropenia is based on age and ethnicity, and classified as mild, moderate or severe [Table 1] [1].

The causes of neutropenia are varied, including bone marrow pathologies such as bone marrow failure syndromes and acute leukaemias, and requires multiple lines of investigations [Table 2] [1]. An important, and well recognised cause of neutropenia is ACKR1/DARC-associated neutropenia (ADAN), formerly known as Benign Ethnic Neutropenia (BEN), which is also associated with the Duffy-null phenotype. ADAN is an inherited condition where people of predominantly African ancestry have a lower ANC than their Caucasian counterparts [2]. Crucially, the lower ANCs seen in ADAN is not associated with increased risk of infection or a propensity to develop haematological malignancies as observed in those with severe congenital neutropenia [2].

There has been interest in characterising ADAN as a variant of normal and to define an ANC reference range for those who have ADAN, including the American Society of Haematology's 'Absolute Neutrophil Count (ANC) by Duffy Status Project' initiative [3,4]. This is due to increasing evidence that redefining ANC in the African population will improve optimal healthcare, allow for greater inclusion in clinical trials and stop unnecessary investigations within this cohort of patients [4].

This review aims to summarise current knowledge of ADAN and proposes new lines of research that could help ameliorate healthcare inequalities experienced by patients from African ancestry living amongst a predominantly Caucasian population such as found in Europe and America.

Table 1. Definition and Classification of Neutropenia.

Age and Ethnicity	Neutropenia (ANC x10^9/L)
From 14 days to 1 yr	<1.0
Children >1 y to adulthood	<1.5
Caucasian adults	<1.8
African / Middle Eastern ancestry adults	<0.5 – 1.5

Classification	Neutropenia (ANC x10^9/L)
Mild	1- 1.8
Moderate	0.5 – 1.0
Severe	<0.5

ANC: *Absolute Neutrophil count*

Table 2. Congenital and Acquired causes of Neutropenia.

Congenital
Isolated severe congenital, cyclical neutropenia
Associated with extra haematological manifestations Barth Syndrome, Charcot-Marie-Tooth neuropathy type B, Cohen syndrome, G6PC3 mutation,GFI1 mutation HYOU1 deficiency, JAGN1 mutation, Kostmann disease, P14/ LAMTOR2, Pearson syndrome, Schimke immuno-osseus dysplasia, SEC61A1 mutation, SMARCD2 mutation, Specific granule deficiency, VPS45 mutation, Wolcott-Rallison syndrome
Associated with immunodeficiency/dysregulation Adenosine deaminase 2 deficiency, ALPS, CD40L/hyper IgM syndrome, Chédiak-Higashi syndrome, CLPB syndrome, FHLH, GATA2 syndrome, Griscelli syndrome, Hermansky-Pudlak syndrome, Reticular dysgenesis, STK4 mutation, WHIM syndrome, Wiskott-Aldrich syndrome, CVID
Associated with metabolic disorders and nutritional deficiency Gaucher disease type I, Glycogen storage disease Ib, Isovaleric, Methylmalonic acidaemia, Propionic acidaemia, Transcobalamin II deficiency
Associated with bone marrow failure Fanconi anaemia, Diamond-Blackfan anaemia, Cartilage-hair hypoplasia, Shwachman-Diamond syndrome, SAMD9/SAMD9L syndromes, SRP54 mutation, Dyskeratosis congenita, U6 small nuclear RNA biogenesis
Acquired
Primary Anti-body mediated: primary auto/allo-immune; **Non-antibody mediated**: Idiopathic neutropenia of infancy CIN/idiopathic cytopenia of undetermined significance-neutropenia
Secondary Hypersplenism, **Infections**: viral (HIV, HCV, HBV, CMV, EBV, HIV, influenza, parvovirus B19, measles, and Sars-Cov-2); Bacterial (*Salmonella, Brucella, Rickettsia, Mycobacterium, Mycoplasma, and H. Pylori*); Parasitic (*Plasmodium spp*, visceral leishmaniasis); Fungal (histoplasmosis); **Autoimmune diseases**: Organ specific (thyroid diseases, inflammatory bowel disease, and primary biliary cirrhosis); Systemic (systemic lupus erythematosus, rheumatoid arthritis including Felty's syndrome, Sjogren syndrome, systemic sclerosis, and graft-vs host disease); **Nutritional deficiencies**: B12, folic acid, iron, copper, and caloric malnutrition; **Immuno-regulatory disorders**: Common variable immunodeficiency, ALPS, ALPS-like diseases, HLH, and macrophage activation syndrome; **Haematologic diseases**: Primary benign (aplastic anemia); Clonal (myeloid malignancies/lymphoid malignancies including LGL); **Drug-induced**: Chemotherapy; Nonchemotherapeutic drugs: analgesics and NSAIDs, antibiotics, antidiuretics, antiretroviral therapy, antithyroids, clozapine, deferiprone, dipyrone, phenothiazines, quinine/quinidine, IVIG, monoclonal antibodies and biological therapies
Likely Acquired
Children/adolescent with neutropenia persisting beyond 5 years

Prevalence of ADAN

In West African populations, the Duffy-null phenotype, characterized by the absence of the Duffy antigen on red blood cells (RBC), is highly prevalent. Studies indicate that its occurrence ranges from 88% to 100%, and its widespread distribution is thought to be due to this phenotype offering a protective mechanism against *Plasmodium vivax* malaria [5].

Although predominantly seen in individuals of African descent, it has also been observed in several other ethnic groups, including Afro-Caribbeans, Ethiopian, Yemenite Jews, Jordanian and Israeli Bedouin populations [6,7]. In addition, the Duffy-null phenotype has been identified in individuals from the United Arab Emirates, suggesting a broader ethnic distribution [8].

Genetics of ADAN

Variations in the ACKR1 gene, which encode the Atypical Chemokine Receptor 1 (also known as the Duffy antigen receptor for chemokines -DARC), are typically associated with ADAN. This receptor is involved in the control of chemokines and is usually expressed on endothelial cells (blood vessel and renal collecting duct), RBCs, as well as lung alveoli and cerebellar Purkinje cells [9]. A specific single nucleotide polymorphism (SNP) T-to-C substitution (rs2814778) in the ACKR1 gene's promoter region is the main genetic defect that causes ADAN [10]. Individuals who are homozygous for the SNP (C/C) leads to the Duffy-null phenotype (Fy−/−), whereby these individuals do not express the Duffy antigen on their RBC surface as described above [11]. This homozygous ACKR1/DARC SNP variation occurs predominately in populations with African and Middle Eastern ancestry [12].

Definition of ADAN

Neutropenia in people of African or Middle Eastern ethnicity is currently defined by ANC <0.5-1.5 x 10^9/L, which would otherwise be classified as moderate-severe neutropenia in Caucasians [Table 1]. However, although ADAN is a recognised phenomenon, there is currently no specific ANC reference range for this group of patients [10]. Furthermore, genomic confirmation of the ACKR1/DARC SNP or Duffy-null phenotype testing is not currently recommended by the most recent European guidelines [1].

Pathogenesis of ADAN

The pathogenesis of ADAN is not completely understood but thought to be multifactorial, involving mechanisms such as altered neutrophil distribution, potential neutrophil auto-antibodies, and the chemokine-regulating functions of ACKR1/DARC [Figure 1].

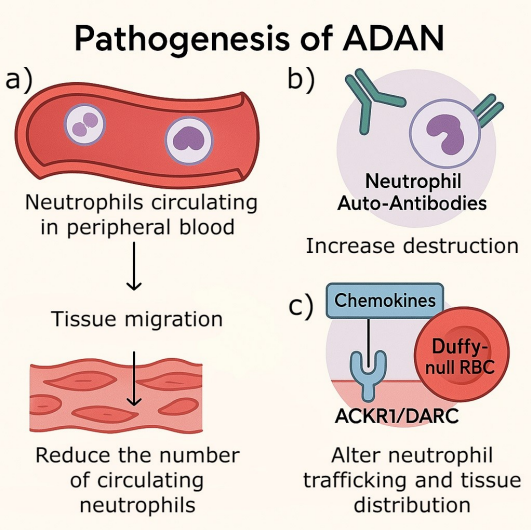

Figure 1. *Cellular mechanisms underlying ADAN.* ***A)*** *Neutrophils migrate to tissues from peripheral blood to reduce absolute neutrophil count (ANC);* ***B)*** *Neutrophil-specific auto-antibody led destruction of peripheral blood neutrophils leads to lower ANC;* ***C)*** *ACKR1/DARC modulates chemokine levels to influence peripheral blood ANC.*

One proposed mechanism suggests that neutrophils in ADAN preferentially migrate to tissues rather than circulate in peripheral blood, leading to reduced peripheral blood neutrophils despite a normal total body neutrophil count. This tissue sequestration may explain the lack of increased infection risk observed in ADAN patients. This hypothesis is supported by studies showing that individuals with ADAN do not experience recurrent infections or an increased susceptibility to bacterial or fungal pathogens [13].

Another potential contributor to ADAN is the presence of neutrophil-specific auto-antibodies, which could lead to increased peripheral destruction of neutrophils and consequently lower peripheral blood ANC. However, the role of auto -antibodies remains controversial, as studies have not consistently detected these antibodies in ADAN individuals [13].

ACKR1/DARC functions as a decoy receptor by binding chemokines without initiating conventional receptor signalling. This mechanism helps regulate neutrophil migration by modulating chemokine levels in circulation [14]. In individuals with the Duffy-null phenotype (those homozygous for the rs2814778 C/C mutation), the absence of DARC on red blood cells reduces chemokine clearance from plasma, which may alter neutrophil trafficking and tissue distribution. This could further explain the reduced ANC observed in ADAN individuals without compromising overall neutrophil function [15].

Clinical presentation and associations with ADAN

As discussed earlier, ADAN is often an incidental finding with patients being referred to secondary care for further investigations. As there is no formal standardised testing used in clinical practice for ADAN, this is often a diagnosis of exclusion and patients undergo extensive investigations including bone marrow biopsy.

Beyond acting as a decoy, ACKR1/DARC regulates chemokine-mediated inflammatory pathways by sequestering pro-inflammatory chemokines, thereby helping to control inflammation. In its absence, as observed in ADAN, this regulation is impaired which could potentially lead to altered immune homeostasis. Importantly, ACKR1/DARC can influence downstream pro-inflammatory signalling, affecting immune responses in various pathological conditions including cancer, infections and autoimmune diseases [14]. Examples have included increased susceptibility to Human Immunodeficiency Virus (HIV) infection, poorer outcomes in breast cancer and higher morbidity and mortality in those with ACRK1/DARC SNP and lung diseases, including acute lung injury and poorly controlled asthma [16].

Absolute neutrophil count in ADAN

ADAN commonly manifests as a mild or moderate neutropenia. However, a recent report from 66 genetically confirmed ADAN cases has shown that the ANC may potentially be even lower than previously recognized (0.1×10^9 - 0.49×10^9/L seen in 9% cases) and would be classed as severe neutropenia [Table 1] [13]. This work also showed a wide range of recorded ANC, with lowest being 0.1 and the highest being 23×10^9/L. ANC elevations (>1.6×10^9/L) often coincided with simultaneously increased plasma C-reactive protein (CRP) levels. Therefore, this does suggest that the ANC in ADAN is fluctuant and a patient's individual ANC range may be highly variable. Given the lack of a validated ANC reference range for ADAN, institutions have started to establish their own ANC range based on assessing their local African patient population for the Duffy-null phenotype and correlating it to the ANC, with one such study recommending an ANC range of 1.21-5.39x10^9/L based on their patient cohort [17].

In the paediatric population, a study based on 49 homozygous cases for the ACKR1/DARC SNP showed that 59% had ANC in the severe range ($0.0\text{-}0.5 \times 10^9$/L) at diagnosis, whilst the median ANC at diagnosis was 0.5×10^9/L. In 72.3% the ANC was within the current reference range during febrile illnesses [18]. The study went on to recommend ACKR1/ DARC SNP testing in all children presenting with isolated neutropenia without severe infections.

Role of ACKR1/DARC in bacterial/fungal, malarial and HIV infections

One of the defining features of ADAN is the observation that it does not lead to increased rates of bacterial and/or fungal infections, giving rise to the concept of it being benign neutropenia [2]. Similarly, as mentioned, ACKR1/DARC is a known receptor for *Plasmodium vivax,* and the Duffy-null phenotype offers a protective mechanism against malarial entry in red blood cells [19]. Interestingly, ACKR1/DARC is also the receptor for HIV-1 on RBC, and influences HIV susceptibility by mediating transfection of HIV-1 and affecting both chemokine-HIV interactions and chemokine-driven inflammation [20]. As a result, individuals with ADAN, and thus lack the ACKR1/DARC receptor, have been shown to have higher rates of HIV-1 acquisition although interestingly survival was unaffected [21].

A possible association between ACRK1/DARC SNP and the severity of COVID-19 infection has also been recently shown. The ACRK1/DARC SNP was more frequently detected among hospitalised COVID-19 patients and the presence of at least one ARCK1/DARC SNP allele was independently associated with death due to COVID-19 [22].

Association of ACKR1/DARC in asthma and acute lung injury

The chronic inflammatory environment in asthma is characterised by chemokine signalling via binding to their receptors including ACKR1/DARC. This receptor plays an important role in cytokine homeostasis in asthma, and the ACKR1/DARC SNP has been associated with worse asthma control and symptoms in those of African descent [23]. Decreased RBC expression of ACKR1/DARC has also been linked to increased IgE in serum samples and higher susceptibility for asthma [24].

It has also been highlighted that African Americans with the Duffy-null phenotype who have acute lung injury were at higher risk of mortality at 60 days and required increased days of mechanical ventilation in comparison to those who were Duffy-positive. One potential reason for this difference was thought to be due to the loss of ACRK1/DARC in these patients, thus causing dysregulation of cytokine homeostasis. This was supported by higher levels of the pro-inflammatory cytokine Interleukin-8 being observed in Duffy-null patients compared to those who were Duffy-positive [25].

Impact of ACRK1/DARC on malignancy

In contrast to severe congenital neutropenia and other inherited forms of neutropenia, ADAN is not known to be associated with an increased incidence of myelodysplastic syndrome or acute/chronic leukaemias [22]. However, this is not the case with breast cancer, where African-American women under the age of 40 experience significantly higher incidence rates of breast cancer compared to Caucasian-American women. African American women also have higher mortality rates from breast cancer at any age, likely linked to the two-fold higher incidence of triple-negative breast cancer in this group [26].

Given the high prevalence of Duffy-null phenotype in the African population, and the role of ACKR1/DARC in modulating chemokines, it has been proposed the Duffy-null phenotype results in dysregulation of chemokine haemostasis leading to a pro-tumorigenic environment and the progression of malignant breast disease [27]. In addition, ACKR1/DARC SNP has been reported to be strongly associated with both the epithelial expression and circulating levels of CCL2 and CXCL8, which are pro-inflammatory chemokines known to be associated with cancer progression [28].

Conclusions

Our review highlights that the ACKR1/DARC and the Duffy-null phenotype has an impact that is broader than expected in people of African ancestry. As previously noted, it is considered a benign variant as the low ANC does not correlate with higher rates of bacterial or fungal infections. However, there is increasing evidence to suggest that the Duffy-null phenotype can impact chemokine, immune and inflammatory regulation which have major implications in the pathogenesis of a number of conditions.

Further research into the molecular consequences of the ACKR1/DARC SNP on chemokine signalling pathways may help to elucidate if the Duffy-null phenotype is linked to the propensity of African populations to have more severe and/or poorer outcomes in conditions such as breast cancer and HIV-1 infection. There is also a need to further clarify if the ADAN genotype is linked to prevalence of autoimmune diseases in this population.

Overall, the ability to distinguish ADAN from Duffy positive neutropenic patients of African descent is important as extensive investigations are justifiably required to rule out pathology in the non-ADAN group. An important goal is to continue to define an accepted ANC reference range for those with ACKR1/DARC SNP, as this can help to improve health care access and reduce inequalities currently found in this cohort of patients. Specifically, an ADAN ANC reference range will facilitate: (i) improved recruitment of people of African ancestry into clinical trials, who may be excluded due to their low ANC; (ii) prevent inappropriate dose reductions in medications/chemotherapy such as observed in patients on clozapine, azathioprine and immunomodulatory drugs in myeloma; and (iii) avoid delays in starting chemotherapy for cancer patients [29-32]. It is notable that genomic studies have highlighted that African patients are more likely to be younger and have more severe forms of cancers, including myeloma, acute myeloid leukaemia and prostate and breast cancers [33-36]. This further emphasises the importance of recognising ADAN as this could help patients gain early access to cancer therapies, including clinical trials, and thus impact cancer outcomes.

Conflicts of Interest

To the author's knowledge there is no conflict of interest involved.

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