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Genetic identification of undiagnosed benign ethnic neutropenia in patients receiving clozapine treatment

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Background

Clozapine therapy presents a risk of agranulocytosis, necessitating monitoring of white blood cell count. The detection of benign ethnic neutropenia (BEN), in which neutropenia can be present without an increased risk of infection, is particularly important in preventing unnecessary withdrawal of clozapine. BEN is strongly linked to the CC homozygote of the single nucleotide polymorphism rs2814778 in the atypical chemokine receptor-1 (*ACKR1*) gene.

Aims

We introduced voluntary genetic testing for BEN in one of our clozapine clinics, with the aim of assessing the prevalence of undiagnosed BEN in patients on clozapine.

Method

We offered genetic testing for BEN to patients undergoing medium- and long-term clozapine treatment, and conducted a comparative analysis of neutrophil counts across three identified groups: those previously diagnosed with BEN, those with newly discovered BEN and those confirmed by genetic testing not to have BEN.

Results

We conducted genetic testing for BEN on 108 patients. Of these, 16 were already registered as having BEN and had the CC homozygote. A further 26 patients (24% of the cohort) who were previously not diagnosed with BEN by standard haematological monitoring were found to have the CC homozygote on genetic testing. Unadjusted mean neutrophil counts were lowest for those with previously diagnosed BEN (2.5×10^9/L, 95% CI 2.2–2.8; $P < 0.001$ *v.* other groups), but those with newly discovered BEN had mean counts that were significantly lower (4.1×10^9/L, 95% CI 3.6–4.7) than those with TT and CT genotypes (5.1×10^9/L, 95% CI 4.7–5.4; $P = 0.006$).

Conclusions

Undiagnosed BEN was common in our naturalistic cohort. The integration of genetic testing into standard monitoring would enhance the management of clozapine therapy, potentially allowing for the safe reintroduction or continuation of clozapine in patients with hitherto unrecognised BEN. All current and prospective clozapine patients should be genetically tested for BEN.

Keywords

Benign ethnic neutropenia; clozapine; pharmacogenomics; ethnicity; neutropenia.

Clozapine remains the only drug of choice for treatment-refractory schizophrenia.[1] The risk of neutropenia and agranulocytosis associated with clozapine therapy is approximately 3 and 0.4%, respectively.[2] Monitoring of white cell count is mandatory in most countries. Clozapine monitoring systems are based on minimum leukocyte and neutrophil thresholds, which can be adjusted for individuals clinically diagnosed with so-called benign ethnic neutropenia (BEN).

BEN

BEN is a historic term – it is also known as pseudoneutropenia, chronic familial neutropenia and benign constitutional neutropenia, among others. It is a condition where neutropenia, defined by normative data in European populations, occurs in people who are otherwise healthy and do not have an increased risk of infection. It was first observed among African American sharecroppers in 1939.[3] BEN is commonly, but not exclusively, observed among people of African and Middle Eastern ancestry.[4] It has been argued that BEN is not an ethnicity-related phenomenon, and would be better termed hereditary or familial benign neutropenia.[4]

Clozapine non-rechallenge

The UK Central Non-Rechallenge Database (CNRD) was established as a safeguard to prevent re-prescription of clozapine to patients who have previously experienced severe neutropenia or agranulocytosis (defined as an absolute neutrophil count (ANC) below 1.5 or 1.0 (BEN) $\times 10^9$/L on two consecutive occasions). This registry is a critical component of the clozapine monitoring system. There are approximately 4000 patients registered on the database.[5] It is of note that much fewer people would be placed on the CNRD if USA guidelines were applied: in the UK, the ANC required for treatment interruption is $<1.5 \times 10^9$/L, whereas in the USA, the threshold is $<1.0 \times 10^9$/L and platelet and white cell count monitoring are not mandated.[6] Recent studies have shown that successful rechallenge is possible in >80% of UK CNRD patients, and that many of these successful rechallenges were in a subpopulation of patients with previously unrecognised BEN.[7,8]

BEN diagnosis

Until recently, diagnosing BEN was essentially a process of exclusion – ensuring that the neutropenia was not caused by other conditions and that neutrophil counts matched the pattern expected for BEN. However, BEN, or more specifically the genetically determined tendency to have lower ANCs, can now be more definitively diagnosed by genetic testing. The CC homozygote of the single nucleotide polymorphism rs2814778 in the atypical chemokine receptor-1 gene (*ACKR1*) (*ACKR1*:c.-67T>C) has very high sensitivity and reasonable specificity for BEN, such that it is thought to be the genetic cause of BEN.[9] The CC genotype abolishes expression of

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the Duffy antigen for chemokines (*DARC*) gene, which leads to the failure to express the *ACKR1* antigen on red blood cells (the so-called Duffy-null phenotype). The Duffy-null genotype is observed in 88–100% of Africans, although only 25–50% of Africans have counts low enough to be defined as BEN (almost all Africans with BEN have the Duffy-null phenotype resulting from the rs2814778 polymorphism).[10] Thus, BEN can be seen as a consequence of lower mean neutrophil counts in people with the CC genotype at rs2814778. In this particular population, there is a left-shift in the distribution of neutrophil counts, such that a threshold count indicative of neutropenia is much more likely to be seen. Regardless of ethnicity, 21% individuals with the CC genotype have a neutrophil count below 2.0×10^9/L, compared with only 1.6% of those with TC or TT genotypes.[11] White Europeans carrying the CC genotype also have relatively low neutrophil counts.[12]

Genetic testing for BEN is not widely used in practice, but one study of 274 people who were prescribed clozapine revealed a very high prevalence of CC genotype carriers in populations with African ancestry taking clozapine.[13] Here, we report on the introduction of genetic testing for BEN in a cohort of people on medium- or long-term clozapine treatment.

Method

All patients attending the Maudsley clozapine clinic (an out-patient clinic serving around 250 patients) for regular haematological monitoring during a 2-month period in early 2024 were offered the option to partake in a genetic test (Myogenes), as part of service improvement programme.

The testing was performed by buccal swab and analysed by HealthInCode (Calle Travessia, 15E, Edificio Biohub, Marina de Valencia, 46024 Valencia, Spain). The rs2814778 variant in the *ACKR1* gene, which encodes the Duffy blood group antigen located on the surface of red blood cells, was captured using a custom probe library (SureSelect Target Enrichment Kit for Illumina paired-end multiplexed sequencing method, Agilent Technologies, Santa Clara, California, USA) and sequenced using the NovaSeq X platform (Illumina, San Diego, California, USA), following Illumina protocols. Participants in the study who were identified as being homozygous positive for the rs2814778 variant, which results in the Duffy-negative phenotype, were classified as having BEN.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human patients were approved by approved by the Drug and Therapeutics Committee at South London and Maudsley NHS Foundation Trust (approval code: DTC/2023/51), which oversees practices related to prescribed medicines in the trust. Written informed consent was obtained from all patients. The consent form was signed by both the patient and the responsible psychiatrist – a prerequisite for testing by HealthInCode. Signed consent forms are securely stored by HealthInCode. Ethnicity was self-reported.

The primary outcome of interest was the number of cases of BEN identified by genetic testing, but not previously diagnosed clinically with BEN. Secondary outcomes related to mean neutrophil counts for groups of patients identified. Three groups were identified and compared: 'known BEN', patients previously diagnosed with BEN; 'new BEN', patients newly identified by the genetic testing; and 'non-BEN', patients without the condition. We compared mean ANC in the past year of haematological monitoring and the lowest ever recorded ANC values between groups. We also compared the number of 'amber' and 'red' events across groups, using standard monitoring criteria (i.e. ignoring the use of modified BEN criteria for those previously diagnosed with BEN). One-way analysis was used to test for significant differences between mean values for the different parameters in the three groups. We used a chi-squared test to compare categorical variables. Analyses of the data were performed with Microsoft Excel 2024 for Windows, SPSS version 29 for Windows and R version 4.3.3 for Windows (The R Project for Statistical Computing; https://www.r-project.org).

Results

In total, 109 consecutive patients were approached, of which one patient declined testing. In the sample of 108 patients, 79 (73.1%) were male. The mean age was 43 years (range 17–77 years). Mean time on clozapine treatment was 147 months (range 3–391 months), or a mean of 12.25 years per patient (1311 patient-years in total). The self-declared ethnic distribution in the sample was as follows: Black, $n = 50$ (46.3%); White, $n = 38$ (35.2%); Asian, $n = 5$ (4.6%); Mixed, $n = 5$ (4.6%) and other, $n = 10$ (9.3%) (see Tables 1 and 2).

Of the 108 patients, there were 16 patients with previously identified BEN (known BEN). All of these cases were confirmed by genetic testing. We identified an additional 26 patients (24.1% of total) with previously unrecognised BEN (new BEN). Another 65 patients did not have BEN (non-BEN) and one patient had been clinically diagnosed with BEN, but they did not have the CC genotype of rs2814778. This patient's data were not used for comparative analysis. This individual was from South Africa and self-identified as White. Her lowest ever recorded neutrophil count was 1.2×10^9/L, and her mean neutrophil count in the previous year was 3.38×10^9/L. Table 1 presents identified BEN groups by ethnicity.

In the known BEN group, 75% (12 out of 16) were male, the mean age was 44.2 (95% CI 36.3–52.1) years and mean time on clozapine was 92.4 (95% CI 56.6–128.1) months. In the new BEN group, 69% (18 out of 26) were male, the mean age was 49.1 (95% CI 43.9–54.3) years and mean time on clozapine was 138.11 (95% CI 96.2–180) months. In the non-BEN group, 75% (49 out of 65) were male, the mean age was 47.1 (95% CI 44.2–50) years and mean time on clozapine was 155.3 (95% CI 129.3–181.3) months. There were no statistically significant differences between identified groups in any parameter (gender: $P = 0.53$; age: $P = 0.49$; time on clozapine: $P = 0.10$).

ANC in different groups

In the group of 107 patients, we analysed 1120 ANC values in total (covering each patient's past 12 months on clozapine), and compared the mean lowest ANC value (at any time when on clozapine) between groups (a total of 1311 patient-years). There was a statistically significant difference in the mean ANC values between the three groups, and in mean lowest ANC ever recorded (Table 2).

Table 1 Benign ethnic neutropenia groups by ethnicity

	BEN status			
Ethnicity	Known BEN	New BEN	Non-BEN	Total
Black	15 (13.9%)	24 (22.2%)	11 (10.2%)	50 (46.3%)
White	1 (0.9%)	1 (0.9%)	36 (33.3%)	38 (35.2%)
Asian	0 (0%)	0 (0%)	5 (4.6%)	5 (4.6%)
Mixed	0 (0%)	0 (0%)	5 (4.6%)	5 (4.6%)
Other	1 (0.9%)	1 (0.9%)	8 (7.4%)	10 (9.3%)
Total	16 (14.8%)	26 (24.1%)	65 (60.2%)	108 (100%)

BEN, benign ethnic neutropenia.

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Table 2 Mean ANC in the past year and mean lowest ever recorded ANC

Group	Mean ANC in past year ($\times 10^9$/L)	Mean lowest ever recorded ANC ($\times 10^9$/L)
Known BEN ($n = 16$)	2.5 (95% CI 2.2–2.8)	1.3 (95% CI 1.12–1.42)
New BEN ($n = 26$)	4.1 (95% CI 3.6–4.7) ($P < 0.001$ *v.* known BEN)	2.1 (95% CI 1.77–2.5) ($P < 0.01$ *v.* known BEN)
Non-BEN ($n = 65$)	5.1 (95% CI 4.74–5.4) ($P < 0.001$ *v.* known BEN) ($P = 0.006$ *v.* new BEN)	2.6 (95% CI 2.42–2.85) ($P < 0.01$ *v.* known BEN) ($P < 0.01$ *v.* new BEN)

ANC, absolute neutrophil count; BEN, benign ethnic neutropenia.

In multiple comparisons between and within groups (using Tukey's honestly significant difference test), there was a significant difference at 95% confidence level. Figures 1 and 2 illustrate the mean value differences between all identified groups, and between the two BEN groups combined and the non-BEN group.

In the group of 16 patients with an existing diagnosis of BEN (known BEN), there were a mean number of 42 conventional amber or red events per patient, compared with 1.4 per patient in the new BEN group ($P < 0.001$) and 1.2 per patient in the non-BEN group ($P < 0.001$). There was no statistically significant difference between new BEN and non-BEN groups ($P = 0.7$).

Discussion

In our cohort of medium- and long-term clozapine patients, we identified a substantial number of cases with the rs2814778 CC genotype that had not previously been clinically diagnosed. These patients exhibited a mean ANC that was lower than that of patients in whom BEN was ruled out, but higher than those with a clinical diagnosis of BEN. As expected, mean neutrophil counts in all patients with BEN were lower than those without BEN. Patients with a clinical diagnosis of BEN experienced a higher mean number of amber and red events than newly identified and non-BEN patients, using standard monitoring criteria.

As outlined, the genetic identification of BEN hinges on the presence of the CC homozygous allele of rs2814778. This single nucleotide polymorphism is located on chromosome 1q23.2, within the promoter region of *ACKR1*, also known as *DARC*. This method has very high sensitivity for detecting BEN.[9,14] Legge et al[14] found that 97% of individuals clinically diagnosed with BEN possessed the homozygous CC allele. Among those with the CC genotype and an ANC between 1000 and 1500 cells/mm^3, only 59% had been clinically diagnosed with BEN. Genetic testing also revealed that 100% of clozapine patients in a Nigerian sample possessed the homozygous CC genotype, but relatively few were clinically diagnosed with BEN.[13]

Unidentified BEN is a leading cause of unnecessarily discontinuing clozapine therapy and of erroneous registration on the non-rechallenge database. At least 79% of patients who had previously experienced treatment-emergent neutropenia and were deemed unsuitable for rechallenge can successfully resume clozapine (successful rechallenge effectively indicates that prior low ANC counts were not clozapine-related).[6,7] It has been estimated that with proper identification of BEN and the use of BEN-adjusted monitoring criteria, up to 95% of these patients might have avoided unnecessary discontinuation.[6,7] Importantly, BEN does not appear to be a risk factor for clozapine-related agranulocytosis, baseline white blood cell counts are not linked to increased agranulocytosis risk in clozapine patients and

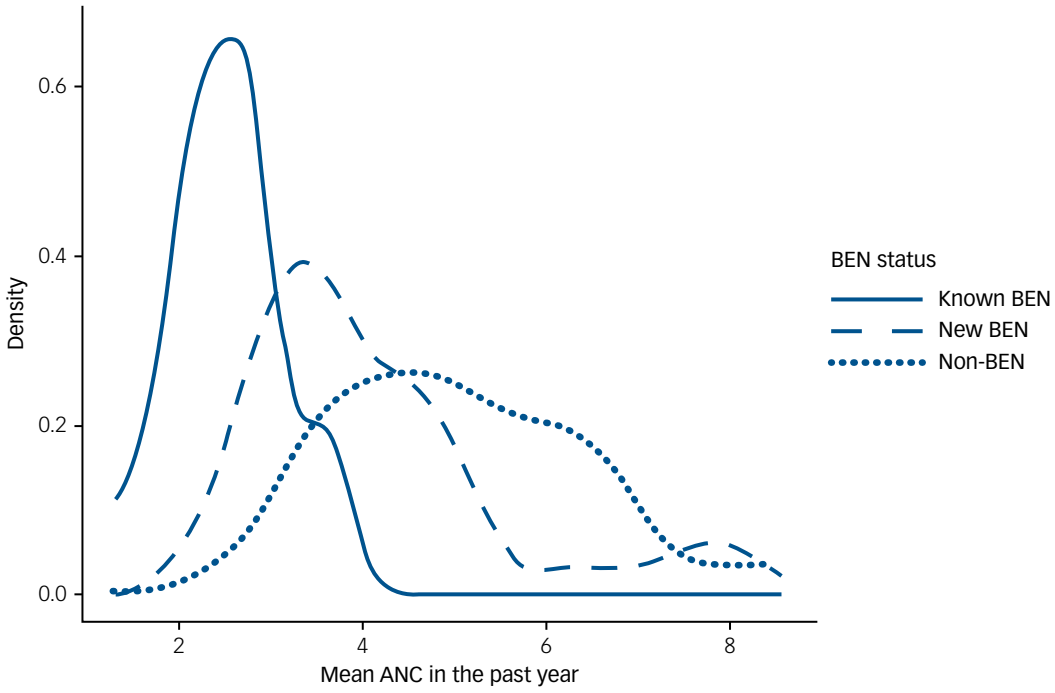

Fig. 1 Scaled density plot for mean values of all groups. ANC, absolute neutrophil count; BEN, benign ethnic neutropenia.

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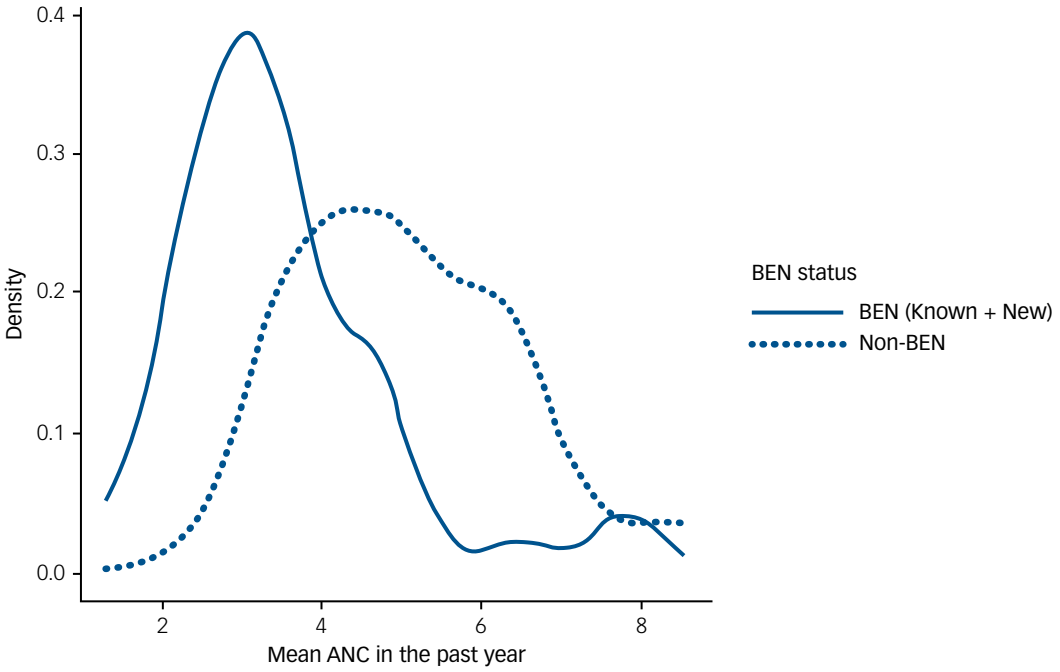

Fig. 2 Scaled density plot for mean values of BEN (known BEN plus new BEN) and non-BEN groups. ANC, absolute neutrophil count; BEN, benign ethnic neutropenia.

agranulocytosis does not occur more frequently among people of African descent.[15,16]

In most countries, diagnosing BEN still involves a comprehensive assessment by a haematology specialist. This assessment considers the patient's ancestry, medication history and evidence of consistently low neutrophil counts in the absence of signs of infection. Given these steps, it is understandable that only a small percentage of patients who need clozapine and have BEN will actually be clinically diagnosed with BEN (as shown in a study of 552 individuals[14]). Our findings highlight a significant limitation in the current diagnostic approach. To initiate the diagnostic process for BEN, patients must first exhibit low ANC, yet our results show that not all carriers of the CC genotype present with sufficiently low ANC levels to provoke investigation. Specifically, our newly diagnosed BEN group had many fewer red and amber monitoring events than those with a clinical BEN diagnosis. Nonetheless, having, on average, lower ANCs than non-BEN patients (that is, a significant left-shift in distribution) puts these undiagnosed patients at a greater risk of registering a low ANC, and therefore at an elevated risk of having clozapine stopped. We suggest that our new BEN patients are the type of patient that ends up on the CNRD for no other reason than their BEN was undiagnosed when a low ANC was recorded.

In a UK study, the average time from initiating clozapine treatment to BEN registration was 2.7 years, and the longest time was 16 years.[6] Ideally, BEN status should be known at initiation of clozapine. By identifying those with the CC genotype at rs2814778, medical professionals can register patients for the lower threshold monitoring, preventing the unnecessary cessation of clozapine therapy and lessening the need for frequent, potentially distressing haematological assessments and invasive investigations into the causes of neutropenia. Furthermore, abrupt clozapine discontinuation because of low neutrophil counts has been linked to severe withdrawal symptoms and reduced or delayed response on treatment resumption.[6]

The main limitation of this study is that data are derived from a relatively modest sample size of 108 patients within a single unit in London. The ethnic composition of this cohort may not reflect the diversity seen in other regions of the UK or globally. A second limitation is that we report observational findings of a service development programme rather than those of a prospective study designed to have wider implications. That is, we did not set out to discover the extent of undiagnosed BEN in our population, and so our method was not designed for this purpose. A final limitation is that our naturalistic clinic cohort is likely to have undergone some degree of selection over the time period during which people were prescribed clozapine. For example, non-responders and those with frequent low blood counts who were not classified as BEN would probably have stopped clozapine before the time of our analysis.

The key question raised by our findings is this: can we continue to prescribe clozapine without full-scale genetic testing for rs2814778 genotype? With the currently available, low-sensitivity clinical methods for identification of BEN, it seems unethical not to use genetic screening for BEN, especially within certain ethnic groups or in those with low baseline ANC. People from ethnic minority groups (which include people of African descent) are more likely to have to discontinue clozapine treatment and, notably, are also less likely to be initiated on clozapine in the first place.[16–18] Genetic screening for rs2814778 genotype would go some way to reducing the extent of these inequitable practices.

That genetic screening should be done for people of African descent is perhaps unarguable, but a case could be made for screening in all individuals regardless of ethnicity, on the basis that self-reported ethnicity is not a particularly reliable indicator of BEN[19] and because the rs2814778 CC genotype is seen in several other familial groups.[12,20] Around one in 65 UK residents has the CC genotype,[11] and it is a common cause of idiopathic neutropenia in European populations.[12] Therefore, we recommend that all current and prospective clozapine patients undergo genetic testing for rs281477 status.

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Data availability

The study data-sets contain health data and are not publicly accessible to ensure patient privacy. Researchers interested in accessing the anonymised patient data can do so by contacting the corresponding author, D.T.

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Author contributions

H.A. designed the study, conducted data analysis and drafted the manuscript. K.V. was responsible for patient identification and drafted the manuscript. B.B. was responsible for patient identification, obtaining patient consent and obtaining DNA samples from patients. D.T. conceived the study, designed the study and drafted the manuscript. All authors approved the final manuscript for publication.

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