Title

Anterior ischemic optic neuropathy and hematological malignancy: a systematic review of case-reports and case-series

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ABSTRACT

Objectives. Demographic and clinical characteristics associated with non-arteritic anterior ischemic optic neuropathy (NAION) are well described. Patients with hematological neoplasms may share some of these characteristics and it may be clinically useful to better understand this set of patients. Our objective is to systematically review the characteristics of patients with both hematological malignancies and NAION.

Design. Systematic review.

Participants: Patients with NAION diagnosis related in time to a haematological neoplasm.

Methods. Data sources: MEDLINE, Web of Science, LILACS, SciELO and OpenGrey. Study eligibility criteria: Case-reports and case-series.

Results. We found 261 records, with 15 studies included plus our case-report. A total of 19 patients (8 female) with mean age of 54,6 years (range 12-87) were analysed: 37% (7) non-Hodgkin lymphoma; 26% (5) myeloproliferative neoplasms; 21% (4) myelodysplasia; 16% (3) leukemias. Limitations: Verification bias, inability to test statistical association between NAION and hematological neoplasms, small number of cases and confounding factors related to medical history and specific interventions in each case limited the robustness of our conclusions.

Conclusions. Our results identified the characteristics of patients with NAION and hematological neoplasms related in time. Further observational studies may enlighten the importance of looking for evidence of an occult neoplastic disorder in patients presenting with NAION. A prompt diagnosis would be of invaluable significance for the best management, in terms of follow-up and therapeutics.

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Keywords: Anterior ischemic optic neuropathy, hematologic neoplasm, systematic review, case report.

1. INTRODUCTION

1.1. Rationale

Ischemic optic neuropathy (ION) is the most common acute optic neuropathy in patients over the age of 50[1]. The ischemic injury may be localized to the anterior part of the optic nerve – anterior ischemic optic neuropathy (AION) or to its retrobulbar portion – posterior ischemic optic neuropathy. There are two etiologic forms of AION: arteritic and non-arteritic. The first is related to giant cell arteritis and represents 5-10% of the cases and the latter accounts for the remaining 90-95% of cases[1, 4, 5]. Although the exact mechanism is not completely understood, the proposed etiology of non-arteritic AION (NAION) is ischemia of the optic nerve head in patients with cardiovascular risk factors[1, 2, 3].

Cross-sectional studies have estimated the prevalence of systemic diseases that might predispose to NAION 6, 7N and hematological malignancies8, 9 results of previously published case-reports and case-series in order to better understand the specific characteristics - including diagnostic, management and prognostic features - of patients who shared the diagnosis of NAION and hematologic malignancy.

1.2. Objectives

To report the case of a patient with a hematological malignancy and NAION, and to conduct a systematic review of previously published cases of hematological malignancies related in time with NAION, discussing its potential implications.

2. METHODS

Our systematic review protocol was registered with PROSPERO (CRD42015019360) and written accordingly to PRISMA-P statement[10].

2.1. Case report

The case report was set up after patient consent as defined by the ethical guidelines at Centro Hospitalar Lisboa Norte, Portugal. Written informed consent was obtained. Data were collected retrospectively after appraisal of medical records. For the purposes of case reporting we followed CARE guidelines[11].

2.2. Systematic review

The systematic review was conducted in line with PRISMA[12] statement. Statistical data respected SAMPL guidelines[13].

2.2.1. Eligibility Criteria

Case reports and series reporting original data of i) adult and pediatric cases of ii) NAION related in time to a haematological neoplasm were accepted. Other study types were excluded. Only published data were accepted. No study was dismissed due to lack of quality, language or time restrictions.

2.2.2. Definitions

NAION was defined as an ischemic neuropathy of the optic nerve, a clinical entity characterized by sudden and permanent loss of vision, optic disc edema or, alternatively, an atrophic appearance of the optic nerve head 1-2 months after the initial loss of vision[14, 15].

We used the WHO definitions for all the haematological conditions described[16].

For data extraction and analysis the above-mentioned definitions were followed. Nevertheless, for the study selection process definitions akin to these were allowed.

2.2.3. Information Sources

We searched MEDLINE, Web of Science, SciELO and LILACS. Grey literature was searched via OpenGrey. The last search occurred on April 2015. Reference lists of relevant studies were also scanned.

2.3.4. Search Strategy

A highly sensitive filter was used to retrieve observational studies [17].

The search strategy was restricted to humans participants.

The developed search strategy for all databases combined the terms (anterior ischemic optic neuropathy) with (hematologic neoplasms OR lymphoproliferative disorders OR leukemia OR lymphoma OR plasma cell neoplasms OR myelodysplasic-myeloproliferative diseases OR myelodysplastic syndromes OR myeloproliferative disorders) *(supplementary file 1).*

2.3.5. Study Records

2.3.5.1. Selection Process

GD and DS independently screened the titles and abstracts yielded by the search against the inclusion criteria. They obtained full reports for all titles that appeared to meet the inclusion criteria or in cases of any uncertainty. GD and DS then independently screened the full text reports and decided whether these meet the inclusion criteria. Additional information was sought from study authors where necessary to resolve questions about eligibility. Disagreements were resolved through discussion, with FR serving as the final arbitrator. None of the review authors were blind to the journal titles or to the study authors or institutions.

The Cohen's kappa (κ) coefficient was used to calculate the inter-observer bias in accordance to Higgins and Deeks, 2011[18].

2.3.5.2. Data Collection Process

GD and DS extracted data in duplicate from the included studies to a pre-piloted electronic form. In case of irresolvable disagreements, these were adjudicated by FR.

RESULTS

Case Report

A 76-year-old Caucasian man with a myelodysplastic syndrome presented to the emergency department with a two-week history of progressive fatigue and recent blurred vision in the right eye. Clinical examination was unremarkable. Blood analysis revealed leukopenia, thrombocytopenia and myeloid blast forms (>20%). Further investigation revealed hepatomegaly and splenomegaly. The diagnosis of secondary acute myeloid leukemia (AML) was made. The patient was proposed for a FLAG chemotherapy regimen followed by hydroxyurea. Ophthalmological evaluation in the emergency department revealed sectorial edema of the optic nerve head and the patient was referred for investigation. On observation, best-corrected visual acuity (VA) was 20/80 OD and 20/24 OS. A right eye relative pupillary afferent defect was present. On fundus examination, a pale right optic disc was observed (figure 1). Left eye was normal. Right eye macular optic coherence tomography (OCT) showed atrophy of the internal retinal layers. Peripapillary nerve fiber layer OCT exposed atrophy in the inferior quadrants (figure 2). Visual fields revealed a unilateral superior arcuate defect in the affected eye, being normal in the fellow eye. A thorough investigation excluded inflammatory and infectious etiologies. The diagnosis of an anterior ischemic optic neuropathy was made and the patient was

proposed for risk factor control and regular ophthalmologic follow-up. At 6 and 12 months follow-up, the AML was stable on hydroxyurea. Clinical findings, VA and OCT remained unchanged.

The diagnosis of an anterior ischemic neuropathy related in time with the acute myeloid leukemia compelled us to systematically review this topic.

Study Selection

The electronic search provided 261 citations. One further citation was added after hand search. After deduplication 233 citations remained - 206 of these were excluded by screening the abstracts for the inclusion criteria. The degree of concordance between screeners was moderate: k=0.5442 (95% CI: 0.418–0.671). Two studies were excluded because full texts were not available, after contacting the authors[19, 20]. The 27 remaining citations were analyzed in their full text form for additional information. Of these 12 were excluded. A total of 15 studies (18 patients) - 13 case reports and 2 case series - met the inclusion criteria[21-35] (figure 1). We also included our current case report for the final analysis, yielding a total of 19 patients.

Study Characteristics

All included studies were in English. The countries of origin for the 19 individuals identified for the final analysis were: 4 (21%) from the United States of America; 3 (16%) from each of Greece, Switzerland and the United Kingdom; and 1 (5%) from each of Canada, India, Morocco, Oman, Portugal and Taiwan. The years of publication varied from 1990 to 2013. Table 1 summarizes study and demographic characteristics.

Demographic Characteristics

The included studies yielded 19 patients, 8 (42%) of whom were female. The mean age was 54.6 years (range:12-87).

Hematologic neoplasm data

Of the 19 patients, 7 (37%) had a non-Hodgkin lymphoma, 5 (26%) had a myeloproliferative neoplasm, 4 (21%) had a myelodysplastic syndrome and 3 (16%) had a form of leukemia. One of the patients classified as having a MDS later converted into an AML before presenting with NAION. Of the total, 8 (42%) patients had NAION diagnosed before the diagnoses of their hematologic neoplasms. Ten (53%) patients had the hematologic neoplasm diagnosed before the NAION and in one patient this information was no specified. In the cases where the hematologic

neoplasm was diagnosed before the NAION, the time elapsed before NAION ranged from 60 days to 7 years. Nine (47%) patients died within a year of NAION diagnosis, while 7 (37%) underwent remission/stabilization. Of the patients firstly diagnosed with NAION, the diagnosis of hematologic malignancy ranged from 10 days to 4 months afterwards. Outcome data were not provided for 3 (16%) patients.

Ophthalmologic data

The presenting ophthalmologic symptom was acute loss of vision in all cases. The mean VA at presentation was 20/120. During follow-up, VA improved in 6 (32%) patients, worsened in 4 (21%) and remained stable in 5 (26%). Four (21%) patients were lost to follow-up. Last documented VA was 20/60. An afferent pupillary defect was found in 15 (79%) patients and was not described in the remaining 4 (21%). Of all patients, 9 (47%) had an initial simultaneous bilateral presentation, and 4 (21%) had sequential bilateral NAION diagnosis. Optic disc edema was present in 17 (90%) cases and absent in 1 (5%), being unmentioned in one. A pale disc appearance was present in 12 (63%) cases and not defined in 6 (32%). A crowded disc (or disc-at-risk appearance) was described in only one patient. Furthermore, 8 (42%) patients had disc haemorrhages. Fundus fluorescein angiography was abnormal in 6 (32%) cases, demonstrating delayed arterial filling and confirming the optic disc edema. It

was not reported in the remaining 13 (68%) patients. Visual field examination revealed a generalized depression in 7 (37%) cases, an arcuate scotoma and an altitudinal defect in 2 (10%) cases each, and unspecific findings in the remaining 2 (10%). Visual field examination was not mentioned in 7 (37%) reports. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were both in the normal range values in 7 (37%) patients, were both elevated in 2 (10%) and were not reported in 7 (37%) cases. ERS was isolatedly high in 2 (10%) patients and CRP in 1 (5%). Table 2 summarizes clinical data.

Medical Interventions

Ten (52%) patients had a history of corticosteroid use before or at the time of NAION diagnosis. Ten (52%) patients had a history of antineoplastic agent use before or at the time of NAION diagnosis. Five (26%) patients had a history of using a form of immunosuppressive therapy before or at the time of NAION diagnosis. No other medical intervention was present consistently across the included studies.

Other systemic diseases

Some accepted risk factors for NAION development include systemic microvascular risk factors (e.g. systemic hypertesion and diabetes).[1] In thirteen (68%) patients,

there was no concurrent systemic medical illnesses assumed as potential risk factors for NAION. Table 2 summarizes the systemic diseases of remaining patients, besides the hematologic neoplasm.

DISCUSSION

Summary of evidence

Although based on an underreported sample of the number of patients with either condition, our results describe the demographic and clinical characteristics of a cluster of patients who share the diagnosis of both a NAION and a hematologic neoplasm. For all the 19 patients included and described in this systematic review there was a clear relation in time between these entities.

Which comes first: optic neuropathy or the hematologic neoplasm?

Intriguingly, eight (42%) patients had NAION diagnosed before the diagnoses of their hematologic neoplasm. As we mentioned before, the time elapsed from the NAION to the hematologic malignancy diagnosis ranged from 10 days to 4 months. However, this may be inaccurate in the sense that the NAION could be a manifestation of a still non-diagnosed hematologic neoplasm. This finding raises the hypothesis of the potential for earlier diagnosis of hematological disease following an optic nerve ischemic event.

It is also important to discuss the causal mechanism involved in such cases where there is an association of these two diseases. We did not find any intervention known to predispose consistently to NAION across cases and merely 10 (52%) of patients

were taking some form of antineoplastic agent. Pathophysiologically, malignancy is well known as a risk factor for prothrombotic states. An increased susceptibility to thromboembolic occlusion of ocular arteries is a possible explanation and its implications are discussed below. In specific hematologic neoplasms, with excess cells in circulation and leukostasis may play the main role for the ischemic event.

Is NAION and hematologic neoplasms different to isolated NAION?

In addition, to better understand the mechanisms of disease, we might be able to find clinical differences in NAION related to different etiologies. Around 95% of NAION have presumed atherosclerotic etiologies[1]. From the 19 patients described, it was not possible to find neither a difference between different neoplasms nor between different medical interventions. Frequencies among gender and age were also not different from other NAION etiologies. As detailed in table 2, thirteen (68%) patients with NAION did not present typical systemic risk factors for development of this clinical entity (i.e. hypertension, diabetes or other). Also, only one patient was described to have a crowded optic disc. Last but not least, simultaneous or sequential bilateral NAION was identified in 9 (47%) and 4 (21%) patients, respectively. This trend for common bilateral disease is not common in published literature.[36] In this regard, one must have in mind that a bilateral NAION without

typical risk factors may be a presenting manifestation a hematologic neoplasm.

However, our conclusions are inevitably limited due to the limited number of patients identified in this study design. Further works, including specific diagnostic tests such as ocular coherence tomography and other imaging modalities could help us to enhance differences and eventually suggest new mechanisms of disease.

In future studies, it would also be relevant to know if different hematological conditions are more prone to ocular prothrombotic phenomena.

Limitations of methodology

Firstly, the very fact that this study was based on case reports and case series is a source of possible bias, namely verification bias.

The relatively small number of gathered cases inevitably limits our conclusions.

As a methodological definition, systematic reviews cannot establish a statistical association, in this case between NAION and hematological neoplasms.

Also, confounding factors related to medical history and specific interventions in each of the cases may have contributed differently for the ischemic events.

Chemotherapy regimens, radiotherapy sessions and age itself need to be controlled and taken into account in different studies with a distinct goal.

Lastly, it is not possible to make conclusions about the influence of the hematologic disease in the ophthalmologic prognosis (see table 3). Many more variables should be included and a different group of comparisons made. Again, further studies can address this relevant question.

Implications for clinical practice and clinical research

Infrequent presentation of a frequent group of diseases

The diagnosis of NAION related in time in hematologic neoplasms may be considered a rare presentation of a frequent group of diseases - hematologic neoplasms. As summarized in table 3, 8 (42%) patients presented with NAION before the hematologic neoplasm in opposition to 10 (53%) patients in whom the neoplasm was diagnosed first. This review identifies the clinical characteristics of patients with NAION and hematological neoplasms related in time. Further observational studies may enlighten the importance of looking for evidence of an occult neoplastic disorder in patients presenting with NAION. Or vice-versa, would it be important to pay attention and screen for painless loss of vision in patients with hematologic neoplasms? Contemporary medical care in developed countries invests a lot in diagnostic testing, to detect disease as early as possible and, hence, increasing chances of treating it effectively. Still, clinical examination and medical

history are more accessible, many times simpler and assuredly cheaper. Using the best scientific and clinical knowledge, we should be alert to promptly diagnose or prevent expected diseases or complications.

Unmet needs

Stated already as a limitation of systematic reviews, larger observational studies are needed to assess whether or not there is an association between these diseases. For this purpose, a case-control study is likely the optimal study design to investigate this question. Additionally, it is also important to investigate if the hematologic disease could be related with the ophthalmologic prognosis. This could be of invaluable significance for better management, in terms of follow-up and therapeutics.

CONCLUSION

Taking all topics into consideration, our review suggests the need to address the infrequently explored and described patients who share hematological neoplasms and ophthalmological vasculopathies such as NAION. A potential change in clinical practice, namely in disease screening and management, would be important in optimizing the care provided for these patients, from diagnosis to treatment.

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Figure Legends

Figure 1 - Colour fundus photography. Optic disc atrophy - more marked in the temporal side.

Figure 2 - Ocular coherence tomography of peripapillary retinal nerve fiber layer (Panels A-D). Inner layers thinning and atrophy predominantly in the inferior quadrants, compatible with the superior visual field defect.

Figure 3 - Flow diagram of the systematic review.

Tables legends

Table 1. Demographic patient characteristics.

Table 2. Clinical characteristics.

Table 3. Summary.