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Etiology of optic atrophy: a prospective observational study from Saudi Arabia

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BACKGROUND: Optic atrophy (OA) represents permanent retinal ganglion cell loss warranting study to establish etiology.
OBJECTIVES: To describe neurogenic causes of OA.
DESIGN: Prospective, observational.
SETTING: Tertiary care center, Riyadh, Saudi Arabia.
PATIENTS AND METHODS: We included consecutive patients of all ages with OA caused by lesions affecting the visual pathways who were referred over a 9-month period (November 2013 to July 2014). Diagnosis was based on visual acuity, ophthalmoscopic features and ancillary tests. Patient demographics, results of a clinical examination, test data and etiology were recorded. For each cause of OA, both gender and age group were analyzed as potential risk factors using simple univariate logistic regression. OA associated with glaucoma and retinal diseases was excluded.
MAIN OUTCOME MEASURE: Description of causes of OA.
RESULTS: Two hundred and four patients and 353 eyes met inclusion criteria. The median age was 27 years (range 3 months-77 years; interquartile range, 27 years) among 111(54.4%) females and 93(45.6%) males, with no statistically significant difference in age of presentation between the genders. The majority of lesions were bilateral (n=151, 74%). Tumors were the most common cause, accounting for 127 (62.2%) cases. These occurred mostly in adults (72.4%) compared to the pediatric group (OR=3.3, 95% CI: 1.79-6.03; *P*<.001). Hereditary neoplasia (OR=5.55; 95% CI: 1.67-18.42; *P*=.005) and metabolic diseases (OR=17.57; 95% CI: 2.15-143.62; *P*=.007) were more common causes in the pediatric group. There were no significant associations between gender or visual acuity and etiology of OA. In developed nations, OA is frequently the result of ischemia and neuritis. We found many other causes, especially orbital and intracranial tumors.
CONCLUSIONS: The frequency of tumors as the cause of OA may represent a higher incidence of aggressive tumors coupled with poor recognition/acknowledgement of symptoms and limited access, resulting in late presentations.
LIMITATIONS: These findings may reflect bias from selective referrals to a tertiary center and may not represent all of Saudi Arabia.

Optic atrophy (OA) is a frequent presentation in the ophthalmology clinics and on the consult service of our tertiary hospital. Although it is not a diagnosis, it represents permanent retinal ganglion cell loss,[1,2] a significant and terminal sign which can be associated with visual impairment (<20/60) and blindness (<20/400)[3] and warrants investigation to establish etiology and pathogenesis. Optic nerve pallor, contraction and loss of fine peripapillary capillaries seen on ophthalmoscopy suggests OA. Further analysis with optical coherence tomography (OCT) of the retinal nerve fiber layer surrounding the optic nerve

can assess the locations and degree of atrophy. Visual field testing is performed to gauge the resulting functional deficits. OA is often the result of ischemic insult or neuritis in developed nations;[1,4-7] in our clinic, we noticed a larger variation of causes of nonglaucomatous OA that included large orbital and intracranial tumors impinging on the visual pathway, primary hereditary forms, inborn errors of metabolism, trauma, autoimmune/inflammatory and iatrogenic causes.

There are few studies looking at the etiologic distribution of OA within a given population[8-15] and to our knowledge none have been conducted in Saudi Arabia. Indeed, studies addressing the causes of blindness and visual disability in the Saudi population are limited and often regional.[16-23] Some of these studies specifically identified OA in their catalog of causes of visual disability.[16,18,20-23] A study conducted in Palestinian children from a population with similar consanguinity rates as Saudi Arabia, found nonglaucomatous OA rates of 12%, second only to primary retinal disorders.[24] A recent Saudi study reported that OA accounted for 28.9% of cases and was the most common cause of low vision in the study population.[16] Although not reported separately from glaucoma, the study helped underscore the prominence of the presentation of OA as a cause of visual impairment and blindness in the Saudi population.[16]

Saudi Arabia is a resource-rich, developing country that offers free healthcare to all its citizens. Healthcare is delivered by separate agencies including the Ministry of Health, universities, various armed forces and National Guard units and private hospitals that are free-standing or within private companies.[25] Despite having advanced medical centers in the large cities with up-to-date diagnostic and therapeutic capabilities that compare favorably with developed nations, delivery of care is neither uniform nor centralized and sophisticated medical care may not be readily accessible to isolated populations in peripheral regions. Furthermore, high consanguinity rates, estimated to be 56%,[25-27] unique socio-cultural issues, environmental exposures, and poor recognition or acknowledgment of symptoms also may contribute to the spectrum and magnitude of disease at presentation. The economic burden of visual impairment and blindness from all causes are felt by the patient, caregiver, healthcare system and community at large. In the pediatric population, there is an additional negative impact on neuro-behavioral development.[28] Our purpose was to elucidate the causes of OA, a common cause of visual disability in this population,[16] as reflected by patients presenting to a large tertiary center.

PATIENTS AND METHODS

This prospective, observational study involved consecutive patients with OA seen by the ophthalmology department at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia over 9 months (November 2013 to July 2014). The study protocol was approved by the institution's research ethics committee. Examinations and investigations were performed according to current standard of care protocols for the management of OA and conducted with ethical considerations, in accordance with the Helsinki Declaration, 2013. Diagnosis was based on visual acuity, ophthalmoscopic features of pale optic nerves and a confirmatory ancillary test. Ophthalmologists were given forms for recording patient demographics, medical record numbers, visual acuity, anterior and posterior segment findings, diagnoses and ancillary examinations. They were encouraged to fill out the forms, provide them to the principle investigators (JNM and MAF) and refer patients of all ages identified with OA to the neuro-ophthalmology clinic for standardization of examinations and investigations (JNM) and to confirm the diagnosis. Full neuro-ophthalmic examinations consisted of Snellen visual acuity, Ishihara color plates, pupil assessments for afferent pupillary defects, extraocular movements, anterior segment biomicroscopy (Haag-Steit AG, Koeniz, Switzerland) and dilated indirect ophthalmoscopy with 78-dioptre and 20-dioptre lenses. Children unable to perform the Snellen visual acuity tests were assessed for their ability to fix and follow and whether their gaze was central, steady and maintained. Ancillary tests including visual fields (Octopus 900, Haag-Streit AG, Koeniz, Switzerland) and time-domain optical coherence tomography (Topcon 3D OCT-2000, version 8.11, Tokyo, Japan) of the optic nerve retinal ganglion fiber layer were performed on all adults and children who were able to cooperate. Visual evoked potential electrodiagnostic testing was performed in children suspected of having OA by direct visualization of pale optic nerves with 20-diopter indirect ophthalmoscopy. All patients had neuroimaging in the form of an MRI of the brain and where indicated, the orbits. Neuroradiology specialists reviewed the neuroimages.

All patients were seen in the ophthalmology clinic as referrals from other departments within the hospital or from outside hospital centers and came with their primary diagnosis already established. Referred patients confined to wards were seen by the ophthalmology consultation service and findings of OA were confirmed by a consultant (JNM). The main reasons for referral were poor vision, pre-intervention baseline examination (prior to neurosurgical and radiation procedures and chemo-

therapy for lesions impacting the visual pathway), post-intervention follow-up examinations and evaluations of genetic disorders known or suspected of affecting the visual pathways and brain. Patients with OA who were seen before and following surgical, medical or radiation therapy were included in the study. To distinguish whether the cause of OA was primary disease or a medical intervention for the disease, we evaluated relevant pre-intervention and post- intervention clinical assessments. Neuroimages were reviewed with the neuroradiology department to corroborate the principal cause of OA. Paper charts and electronic medical records tests were reviewed for all patients and only patients with full assessments and tests confirming OA over the 9-month study period were retained. OA secondary to glaucoma, primary retina and retinovascular diseases were excluded to concentrate on neurogenic causes.

Patient demographics, data from clinical exams and, where possible, octopus visual fields, time domain optical coherence tomography (OCT) measurements of optic nerve retinal nerve fiber layers, visual evoked potentials and neuroradiologic imaging were collected and tabulated using Excel software (Microsoft, Redmond, WA, USA). All patients less than 21 years of age were defined as pediatric to comply with the American Academy of Pediatrics definition. Decimal visual acuity was used to facilitate calculations. Once the patients were de-identified the data were collated and grouped into categories for statistical analysis. These categories were determined according to observed diseases/disorders and if known included autoimmunity, congenital malformation, hereditary metabolic, hereditary neoplasia and other hereditary causes, infections, ischemia/vascular disorders, non-hereditary neoplasia, toxic, and trauma. The dataset was described by disease/disorder category, gender and age groups (adults and pediatrics) with mean, median and ranges of ages. The data was then analyzed using STATA/MP 12 data analysis software (StataCorp LP, College Station, TX, USA). Graphs were generated from both Excel and STATA software. For each cause of OA, both sex (male vs. female) and age group (pediatric vs. adult) were analyzed as potential risk factors using simple univariate logistic regression. Odds ratios and confidence intervals were used to determine the strength of associations. Statistical significance was set at $P<.05$.

RESULTS

Over 9 months, 353 eyes of 204 patients were identified as having OA, meeting the inclusion criteria. As KFSHRC is a specialist tertiary care center, all patients evaluated for this study were referred. The median age for the whole group was 27 years (range, 3 months-77 years; IQR=27 years). All patients were of Middle Eastern origin: 200 Saudis, 3 Syrians and one Egyptian. The non-Saudis had methylmalonic acidemia and were referred by the genetics department for evaluation of optic nerves. There were 111 females (54.4%) and 93 males (45.6%). Adults accounted for 135 (66.2%) and pediatric patients, 69 (33.8%). The median age for adults was 38 years (range: 21-77 years) while the pediatric median age was 12 years (range: 3 months- 20 years) (**Table 1**). There was no statistically significant differences in age of presentation between the genders (P=.15). One hundred fifty-one cases (74%) were bilateral while 53 (26%) were unilateral. Visual acuities varied from 20/20 to no light perception and there was no significant association between visual acuity and the etiology of OA.

The commonest causes of OA were tumors, accounting for 127 cases (62.2%). Hereditary disorders as a group were a distant second with 35 cases (17.1%), while autoimmune diseases (multiples sclerosis, antiphospholipid syndrome, neuromyelitis optica, systemic lupus erythematosus, and neuro-Behcet's), accounted for 26 cases (12.7%). The breakdown of the hereditary disorders group revealed 21 cases (10.2%) that were non-neoplastic and 14 cases (6.8%) that were neoplastic (**Table 2**). Less frequent causes of OA included vascular/ischemic disorders (non-arteritic optic neuropathy, cerebral vascular accidents, sagittal sinus thrombosis and arteriovenous malformation), congenital malformations (hydrocephalus, arachnoid cysts, myelomeningocele and isolated craniosynostosis), infections, trauma and presumed toxicity. Six (4 pediatric and 2 adult) cases of OA were extensively investigated and at termination of the study continued to defy classification and were documented as unknown (**Table 2**) (**Figure 1**). The majority of patients seen (66.18%) were adults and exhibited different etiologies of OA than the pediatric group. The difference in number of

Table 1. Age of patients diagnosed with optic atrophy due to neurologic causes.

	Mean age (years) (median, range)
All patients (n=204)	27 (3 mo-77 y)
Females (n=111, 54.4%)	28 (1.1 y-73 y)
Males (n=93, 45.6%)	25 (3 mo-77 y)
Adults (≥ 21 years of age) (n=135, 66.2%)	38 (21-77 y)
Pediatric (<21 years of age)(n=69, 33.8%)	12 (3 mo-20 y)

Table 2. Causes of optic atrophy by age and gender.

Cause of optic atrophy	Total number (%)	Adult patients	Pediatric patients	Females	Males	Median age (range)
Autoimmune	26 (12.7)	21	5	17	9	28.5 y (11-53 y)
Congenital malformation	5 (2.5)	2	3	1	4	17 y (6-22 y)
Hereditary/ metabolic	9 (4.4)	1	8	6	3	15 y (13 mo-27 y)
Hereditary/ neoplasia[a]	14 (6.8)	4	10	7	7	11.5 y (2-38 y)
Hereditary/others[b]	12 (5.9)	3	9	3	9	14.5 y (18 mo -35 y)
Infection	3 (1.5)	2	1	3	0	23 y (18-35 y)
Ischemia/vascular	12 (5.9)	11	1	5	7	56.5 y (13-73 y)
Non-hereditary neoplasia	113 (55.4)	88	25	67	46	34 y (22 mo-77 y)
Trauma	3 (1.5)	1	2	1	2	17 y (7-31 y)
Toxic	1 (0.5)	0	1	0	1	-
Unknown	6 (2.9)	2	4	1	5	2.4 y (3 mo-49 y)
Number of patients	204 (100)	135	69	111	93	27 years (3 mo-77 y)

[a]Hereditary neoplasias included neurofibromatosis I and II and Von Hippel-Lindau syndrome.

[b]Other hereditary disorders associated with optic atrophy were hereditary optic atrophy, Leber's hereditary optic neuropathy, mitochondrial complex III deficiency, Wolfram's syndrome and isolated craniosynostosis, 21-hydroxylase deficiency and craniofacial disorders (Crouzon syndrome and osteopetrosis)

patients in the two age groups and gender are summarized in **Tables 2 and 3**.

Tumors causing OA were varied in type and location. Non-hereditary tumors accounted for 89% of all neoplasia, were responsible for the majority of all OA (55.4%) and exhibited a bimodal frequency and age distribution similar to the bimodal pattern for all OA (**Figure 2A**). The median age was 34 years (range: 22 months to 77 years). The most common types of tumors were glioma (22.04%), pituitary macroadenoma (22.04%), meningioma (21.26%), craniopharyngioma (6.30%) and leukemia (4.72%). Rarer tumors included nasopharyngeal carcinoma, basal chordoma, pineal germinoma, giant cell tumor, neurocytoma (**Supplement 1**), medulloblastoma, multiple myeloma, rhabdomyosarcoma, chondroblastoma, glioblastoma multiforme, anaplastic ependymoma, Ewing's sarcoma, choroid plexus papilloma, papillary tumor of the pineal region, hemangioma, lymphangioma, pilomyxoid astrocytoma and ovarian metastasis. Neoplasia was most common in adults than pediatric patients (**Table 2**) (**Figure 1**). when compared to other causes (OR=3.3; 95% CI: 1.79-6.03; *P*<.001) and also more likely to result in unilateral OA (OR=3.01; 95% CI: 1.4-6.47; *P*=.005). Further analysis of the common tumor types revealed that gliomas had a greater likelihood of occurring in the pediatric age group (OR=9.34; 95% CI: 2.77-31.54; *P*<.001) without significant disparity between the genders. Meningiomas, on the other hand were more common in adults (OR=10.06; 95% CI: 1.29-78.35; *P*=.027) and females (OR=5.49; 95% CI: 1.75-17.2; *P*=.004). Although pituitary tumors also were more likely in adults (OR=5.09; 95% CI: 1.12-23.14; *P*=.35), they were more likely in males (OR=2.69; 95% CI: 1.13-6.38; *P*=.025). The difference in number of optic nerves affected did not reach statistical significance in all three neoplastic groups.

Hereditary neoplasia (von Hippel Lindau, optic nerve hemangioma and gliomas and meningiomas associated with neurofibromatosis type I and II) accounted for 6.8% of all cases and 11% of all neoplasia. They were observed mostly in the pediatric population (OR=5.55; 95% CI: 1.67-18.42; *P*=.005). Similarly, hereditary metabolic diseases comprising methylmalonic acidemia (**Supplement 2**) and metachromatic leukodystrophy (OR=17.57; 95% CI: 2.15-143.62; *P*=.007) and "other" hereditary diseases including, hereditary OA, Leber's

hereditary optic neuropathy, mitochondrial complex III deficiency, Wolfram's syndrome and isolated craniosynostosis and 21-hydroxylase deficiency and craniofacial disorders (Crouzon's and osteopetrosis) were also most common in the pediatric group (OR=6.6; 95% CI: 1.73-25.51; *P*=.006) (**Figure 2B**). Although all hereditary conditions were most likely to affect both optic nerves when compared to the other causes combined (excluding "unknown") this did not meet statistical significance (OR=1.52; 95% CI: 0.622-3.74; *P*=.36). Like meningioma and pituitary macroadenoma, the "other" hereditary group exhibited gender disparity and this group occurred more in males than females (OR=3.86; 95% CI: 1.01-14.69; *P*=.048). Otherwise, there was no significant association between gender and the etiology of OA.

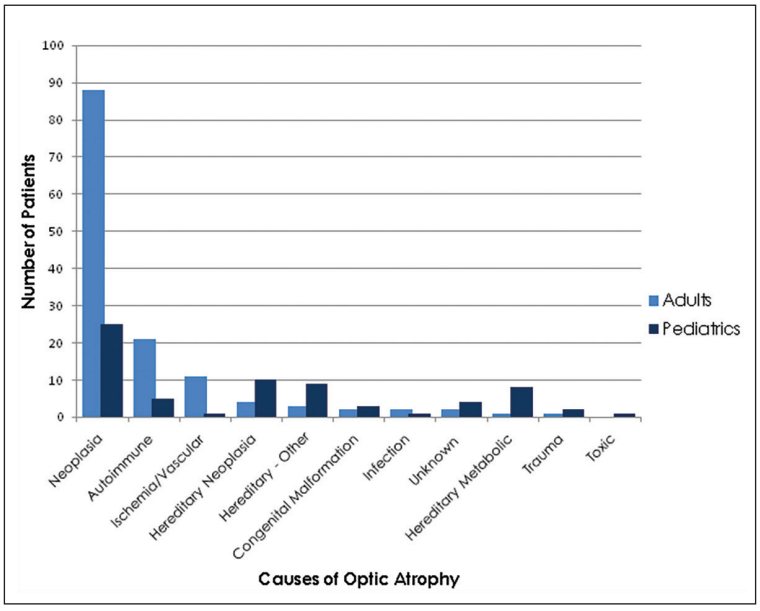

Figure 1. Frequency of neurologic causes of optic atrophy in adult and pediatric groups in the study group (n=204).

DISCUSSION

Optic atrophy, a common cause of permanent visual disability and blindness, is a frequent finding in our center. Our study identified multiple causes including neoplasia, inflammation, heredity, ischemia/vascular, trauma and toxicity. Of these causes, intraorbital and intracranial neoplasia was by far the most common etiology and caused OA by various mechanisms including direct compression and nerve infiltration or secondary to chronic papilledema and obstructive hydrocephalus. Neoplasia was more likely than other causes to cause OA in adults than children. Both hereditary neoplasia, mostly due to neurofibromatosis, and non-hereditary neoplasia were significant causes in both pediatric and adult patients (**Table 2 and 3**) (**Figure 1**). When separated, the non-hereditary neoplasia group displayed the same bimodal pattern of OA as the whole group with peaks in age in mid-20s and 40s (**Figure 2A**). The reason for this bimodal distribution is not clear; however, the occurrence of cancer in a younger age group is a well known phenomenon in Saudi Arabia.[29,30] Indeed, the most common cancers, breast in females and colorectal in males, both occur in younger age groups than in the west.[29,30]

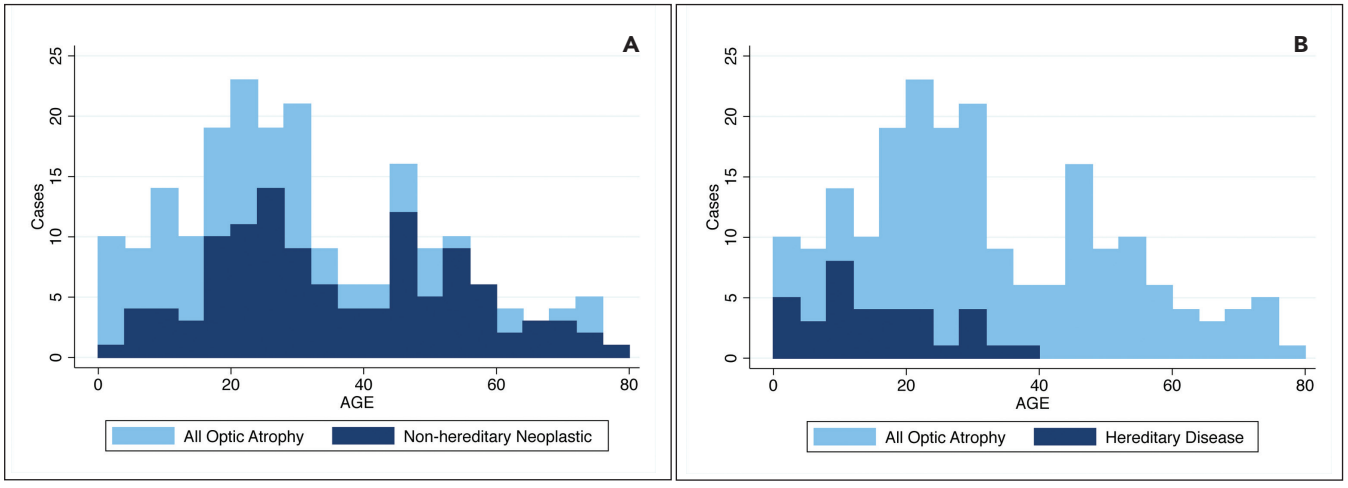

Figure 2: (A) Frequency distribution of optic atrophy due to non-hereditary neoplastic causes in different age groups exhibiting a bimodal age distribution that shadows the bimodal frequency and age distribution for all optic atrophy. (B) Frequency distribution of optic atrophy due to hereditary causes in different age groups compared to frequency distribution of all optic atrophy showing predominant occurrence in younger patients.

Menon et al[13] in their study of 484 patients with OA, found that tumors were the cause in 24.4%. Tumors were also the most common cause in patients less than 40 years of age, accounting for 58.5%. The majority were pituitary macroadenoma, craniopharyngioma, meningioma and glioma. In a study describing the diagnostic yield of evaluations for OA, Lee et al[8] found compressive lesions accounted for only 20% of causes of isolated OA comprising similar tumor types. The majority, 61%, were detected in patients less than 50 years of age. In our study, intraorbital and intracranial tumors accounted for a larger segment of the population at 62.2% with no statistical difference in age of presentation between the genders. As in the previous studies, glioma, meningioma, pituitary macroadenoma and craniopharyngioma were the commonest tumors exhibiting two peaks in young age groups. The median age for all OA, 27 years, was considerably young and can be attributed in part to early onset neoplasia and the hereditary forms that were most common in the pediatric group (**Table 2 and 3**) (**Figure 2B**). A recent annual oncology report from KFSHRC stated that primary malignant neoplasms of the brain accounted for 3.2% of all malignancies in all age groups, which is much higher than in the USA with reports of only 1.4%. In children these malignancies accounted for 16.5% of all malignancies, ranking second only to leukemia (29.5%),[30] findings that comport with our observations. Saudi Arabia has a youthful population with 41.7% of people less than 15 years of age[29] and consanguinity is commonplace with rates that vary regionally from 42.1% to 67.2%.[25-27] These factors along with epigenetic influences on gene expression such as lifestyle, diet, environment (pollution, ultraviolet light exposure, temperature), geography and concurrent medical conditions, such as metabolic syndrome, might contribute to the early onset and types of neoplasia and resultant OA in the younger age group that we observed in our study.

Hereditary causes including autosomal and mitochondrial inheritance were more common in the pediatric group (**Table 2**) (**Figure 2B**). In this group hereditary and non-hereditary tumors accounted for 50.7% of cases of OA and metabolic disorders, 11.6%. In their report, Repka and Miller[11] also found tumors to be the predominant cause of OA in children less than 18 years old, occurring in 29% of cases, where they were able to establish a diagnosis. More recent studies have revealed a shift in etiology with perinatal complications including prematurity emerging as the most common cause of OA.[9,10,15] This has been attributed to improved neonatal survival, albeit with significant morbidity. Although defining their pediatric groups with variable age limits, these studies exposed an evolving trend away from tumors. Interestingly, we only observed four pediatric patients with neurodegeneration, of undefined cause, related to OA. Associated perinatal co-morbidities were not determined. Nonetheless, our population did not reflect this evolution and tumors remained the preeminent cause of OA in children.

The merits of this study include the large sample

Table 3. Risk of optic atrophy by age group and cause category in adult and pediatric patients.

Cause	Age group	Odds ratio 95% (confidence interval)	*P* value
Non-hereditary neoplasia	Adult	3.295 (1.799–6.036)	.001
	Pediatric	0.303 (0.166–0.556)	
Autoimmune	Adult	2.357 (0.848–6.553)	.100
	Pediatric	0.424 (0.153–1.179)	
Hereditary Neoplasia	Adult	0.180 (0.054–0.598)	.005
	Pediatric	5.551 (1.673–18.421)	
Hereditary/ Other	Adult	0.152 (0.040–0.580)	.006
	Pediatric	6.600 (1.725–25.251)	
Ischemia/ Vascular	Adult	6.032 (0.752–47.727)	.089
	Pediatric	0.166 (0.021–1.312)	
Hereditary Metabolic	Adult	0.057 (0.007–0.465)	.007
	Pediatric	17.573 (2.150–143.623)	
Unknown	Adult	0.244 (0.044–1.369)	.109
	Pediatric	4.092 (0.731–22.925)	
Congenital malformations	Adult	0.331 (0.054–2.028)	.232
	Pediatric	3.023 (0.493–18.533)	
Infection	Adult	1.023 (0.091–11.479)	.986
	Pediatric	0.978 (0.087–10.977)	
Trauma	Adult	0.250 (0.022–2.807)	.261
	Pediatric	4.000 (0.356–44.907)	
Toxicity	No adult cases		

Simple univariate logistic regression analysis was used to determine the association between age group and category of cause of optic atrophy. There were differences in causes between the age groups. Non-hereditary neoplasia was the most likely cause of in adults while all hereditary categories were the most likely cause in the pediatric age group (<21 years of age). There were no statistically significant differences in age between causes in the other categories. OR=odds ratio; CI=confidence interval

size, prospective and consecutive compilation of data, clinical verification of OA and consultant neuroradiology confirmation of associated neuroimaging. The finding of tumors in younger patients is consistent with previous oncology reports in this region.[29,30] This study contributes to the limited knowledge of etiology of OA within any given population and to our knowledge is the first study of its kind in Saudi Arabia. The main limitations include its brevity and location. Our results may represent the demographics and distribution of causes of OA over the time period studied at this particular hospital and this might not reflect the true distribution for all of Saudi Arabia. KFSHRC is the main oncology hospital for Saudi Arabia, is affiliated with the largest pediatric oncology center and is recognized as the most advanced cancer center in the Middle East and North African region. Although patients were referred from all regions of Saudi Arabia, the high incidence of oncologic etiology in children and adults might have resulted from a referral bias. Our study might only be describing the types of patients referred to KFSHRC. A long-term, multicenter study might well result in a different, more representative distribution of neurologic causes of OA and include different types of tumors and hereditary disorders. Additionally, intercurrent medical, social (ethnicity, socioeconomic, smoking, lifestyle, diet) and drug intake history, province of habitation (different geographic and environmental exposures), consanguinity and regional traditions/cultural mores were outside the scope of this study. Race, ethnicity and low socioeconomic strata appear to be independently associated with increased vision loss that includes preventable causes with known risk factors and causes that are amenable to surgical and medical intervention.[31] Thus more comprehensive information about our patients might have helped to explain our particular findings. In their study of intracranial meningioma, Jallu et al[32] found a higher incidence, larger tumors and a larger proportion of patients (44.2%) presenting with unilateral or bilateral blindness when compared to the west. They attributed their findings to lack of insight and unique cultural restraints that lead to late presentations in this population.

In conclusion, ischemic/vascular and autoimmune causes, the most common causes of neurological OA in the West, were found to be less frequent in our population. Our study found that orbital and intracranial tumors were the most common cause of OA and occurred in younger patients when compared with the United States. Hereditary disorders were expected to be frequent in a region of high consanguinity and ranked second to tumors. Although the high rate of tumors may have resulted from mostly complicated, advanced case-referrals to a specialist hospital, it may also represent a high incidence of aggressive tumors coupled with poor access and poor recognition, acknowledgement and response to symptoms, resulting in late presentations in the studied population. Future more comprehensive, multicenter studies are needed to provide more representative data for this region. Furthermore, careful evaluation of contributions from genetic susceptibility, cultural, environmental and lifestyle factors and access to advanced medical care might be useful for developing tailored public health interventions aimed at reducing permanent vision loss.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Supplemental Example Cases

Supplement 1: Central neurocytoma. A 24-year-old male presented with severe headaches, nausea, vomiting and poor vision.

Supplement 2: Methylmalonic acidemia. 15-year-old female with genetically determined methylmalonic acidemia, chronic renal failure and developmental delay presented with poor vision after multiple metabolic acidotic crises.