

Potpourri of retinopathies in rare eye disease – A case series

Neelam Pawar, George J Manayath¹, Shishir Verghese¹,
Prithvi Chandrakanth¹, Virna Shah², Ashwini Raut²,
Swarna Gaikwad³, Parth A Patil⁴,
Mansha Daswani², Meenakshi R,
Kalpana Narendran⁴, Venkatapathy Narendran¹

This case series describes the ocular and retinal manifestations of rare eye diseases in systemic syndromes. This observational case series consists of five patients with varied ophthalmic manifestations and documentation of imaging in rare pediatric and adult retinopathies. Two patients had Kearns Sayre syndrome (KSS) based on the classical triad of external ophthalmoplegia, pigmentary retinopathy, and onset before 20 years of age. In one patient of KSS, the mitochondrial retinopathy was seen in an asymmetric pattern, and the second patient presented with KSS after being mis-diagnosed as myasthenia gravis elsewhere. A case of Senior Loken syndrome in pediatric age is described in this series with varied ophthalmic manifestations ranging from retinitis pigmentosa to orbital abscess. This series also enlightens features of Hallervorden Spatz syndrome presenting with bull's eye maculopathy and a case of spino-cerebellar ataxia type 7 presenting with pigmentary retinopathy.

Key words: Hallervorden Spatz syndrome, Kearns Sayre syndrome, pigmentary retinopathy, Senior Loken syndrome, spino-cerebellar ataxia type 7

Rare eye diseases (REDs) are the major leading causes of visual impairment and blindness for children and young adults worldwide. These eye diseases occur either isolated or as a part of syndromic anomalies. These heterogeneous groups of conditions can range from relatively prevalent disorders such as retinitis pigmentosa (RT) to very rare retinopathy entities.

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Pediatric Ophthalmology and Squint Services, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Tirunelveli, ¹Department of Retina & Vitreous Aravind Eye Hospital & Postgraduate institute of Ophthalmology, Coimbatore, ²Department of Neuro-ophthalmology, Aravind Eye Hospital & Postgraduate institute of Ophthalmology, Coimbatore, ³Mahatma Gandhi Eye Hospital, Nagpur, ⁴Department of Pediatric Ophthalmology & Strabismus Aravind Eye Hospital & Postgraduate Institute of Ophthalmology, Coimbatore, India

Correspondence to: Dr. Shishir Verghese, Retina Services, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Coimbatore, India. E-mail: shishirverghese@gmail.com

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Pediatric ophthalmologists and medical retina specialists are usually the first to encounter REDs. Timely diagnosis enhances the understanding of the disease and management of these retinopathies for early visual rehabilitation. Herein, we describe a series of five cases of REDs with retinopathies in pediatric and young adults.

In this case series, we describe various retinopathies in Kearns Sayre syndrome (KSS), Senior Loken syndrome (SLS), Hallervorden Spatz syndrome (HSS), and spino-cerebellar ataxia (SCA) type 7.

Case Reports

Case 1

A 20-year-old female presented with complaints of decreased vision in the right eye (RE) for 5 years along with drooping of both eyelids for 10 years. On examination, her RE best-corrected visual acuity (BCVA) was 6/24, and in the left eye (LE), it was 6/9. Ocular adnexal examination showed moderate ptosis in both eyes (BE) along with complete ocular motility restriction [Fig. 1a]. Anterior segment examination in BE was unremarkable. Fundus examination of the RE showed multiple large well-circumscribed patches of retinal atrophy with scalloped edges and areas of speckled retinal atrophy. The LE fundus revealed a salt and pepper pattern of appearance with a few areas of patchy retinal atrophy [Fig. 1b and c]. Multi-modal imaging (MMI) was performed, which included fundus auto-fluorescence (FAF) and optical coherence tomography angiography (OCTA) [Fig. 1d-g], which confirmed an asymmetric pattern of retinopathy between and BE spectral-domain optical coherence tomography (SD-OCT) [Fig. 1h-m].

General physical examination revealed short stature along with wasting of limb muscles and associated weakness. She complained of speech disturbances, deglutition difficulty, unsteadiness of gait, and a few episodes of syncope. A cardiac evaluation revealed a complete heart block, for which she underwent permanent pacemaker implantation. Magnetic resonance imaging (MRI) of the brain as well as a magnetic resonance (MR) spectroscopy revealed extra-ocular muscle thinning as well as diffuse neuro-parenchymal volume loss with mild cerebellar atrophy. Hematological workup revealed elevated plasma creatine phosphokinase and lactate levels. Myotonic dystrophy and myasthenia gravis were ruled out in view of absent limb weakness or clinical myotonia, and the electro-myographic studies and repetitive nerve stimulation tests were normal. Additionally, the acetylcholine receptor and muscle-specific tyrosine kinase antibodies were negative. She was diagnosed with KSS based on the clinical diagnostic criteria, which include the triad of progressive external ophthalmoplegia, pigmentary retinopathy, and onset before

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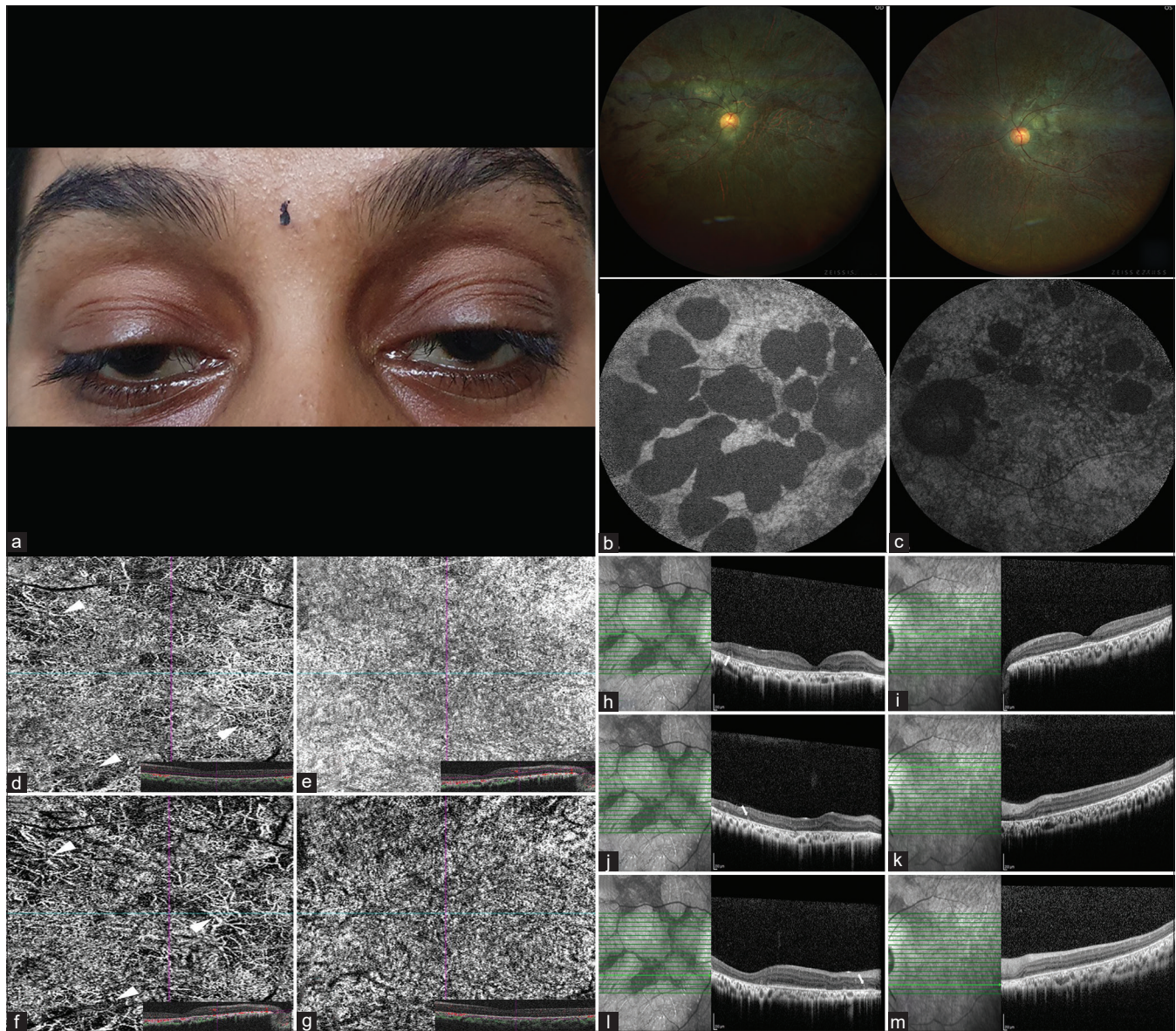


Figure 1: (a) shows bilateral ptosis in case 1. (b and c) show fundus and FAF in RE and LE with more atrophic patches in RE and more hypo-florescence in FAF than in LE. (d-g) RE OCTA showing loss of choriocapillaris with visible larger deeper choroidal vessels (arrowheads). (d) LE at the level of the outer retina-choriocapillaris complex showing choriocapillaris sparing (e). RE OCTA with areas of choriocapillaris loss (arrowheads) (f). LE OCTA showing an intact choriocapillaris (g). (h-m) OCT of RE and LE showing photo-receptor loss and tubulation more in RE (arrowheads) than in LE, respectively

20 years of age along with the presence of heart block and cerebellar ataxia.

Case 2

A 10-year-old female patient presented with complaints of drooping of eyelids and decreased vision in BE for the past 2 years. Her parents noticed impaired hearing and generalized weakness. The family history was unremarkable. A general physical exam revealed short stature. The BCVA was 6/18 in BE. Extra-ocular movements were full with end gaze nystagmus. Bilateral moderate ptosis was noted with poor Bell's [Fig. 2]. Anterior segment examination was unremarkable. Fundus examination in BE showed pigmentary changes with optic disc pallor. Myasthenia gravis was ruled out after a negative acetylcholine receptor antibody test

(<0.11 nmol/L). Electro-myography (EMG) did not suggest any evidence of neuro-muscular abnormality. Repetitive nerve stimulation (RNS) study was suggestive of post-synaptic myasthenia syndrome. She underwent multi-disciplinary consultation with the cardiologist, neuro-psychiatrist, and endocrinologist and underwent muscle biopsy and genetic analysis. Muscle biopsy showed ragged red fibers on trichrome staining. She had right bundle branch block. These findings along with the history were suggestive of KSS. She was advised to use low vision aids, and parents were counseled regarding morbidity and regular follow-up.

Case 3

A 9-year-old girl presented for a routine ocular examination. She had a history of chronic kidney disease (CKD) with stage 4

hypertension. She also had a history of juvenile nephronophthisis and was undergoing peritoneal dialysis and diagnosed with Senior Loken syndrome (SLS). Her BCVA in BE was 6/18 with anterior segment findings being unremarkable. Fundus examination revealed BE RP. She was advised observation and routine follow-up. Four years following the initial exam, she presented with complaints of decreased vision with BE having only hand movement (HM) vision. Fundus examination revealed retinal detachment in RE and RP with exudative retinal detachment, suggestive of Coats-like syndrome in LE [Fig. 3a and b]. SD-OCT in BE showed serous retinal detachment along with photo-receptor cilia disorganization in the RE. The external limiting membrane (ELM) and photo-receptors were absent in the LE. She developed neo-vascular glaucoma (NVG) subsequently, and her intra-ocular pressure increased after every episode of hemodialysis in RE. Diode laser cyclo-photo-coagulation and intra-vitreous injection of bevacizumab were given for a painful blind RE. She was initiated on topical anti-glaucoma medications, steroids, and mydriatics after the procedure. On subsequent visits, she was comfortable, although with poor vision. On her last follow-up, she presented with painful RE proptosis consistent with an orbital abscess which was treated successfully [Fig. 3c].

Case 4

A 16-year old male presented with complaints of night blindness since childhood. He had a history of difficulty in maintaining balance while walking for 7 years and speech difficulty for 10 months. He was born of consanguineous marriage, with no family history of similar complaints. General examination revealed a protruding tongue with dysarthria and ataxia with decreased intellectual ability. Ocular examination revealed blepharospasm with mild ocular movement restriction in all gazes associated with nystagmus. Anterior segment examination in BE was unremarkable. Fundus examination

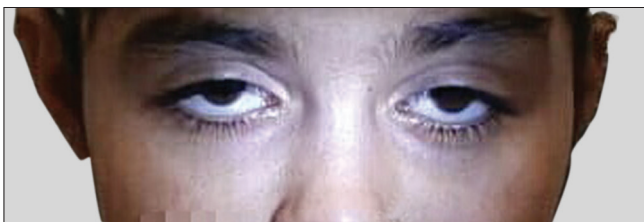


Figure 2: Bilateral ptosis in KSS (Case 2)

of BE revealed optic disc pallor with bull's eye maculopathy and pigmentary retinopathy [Fig. 4a and b]. The MRI of the brain revealed symmetrically altered signal intensity in bilateral antero-medial globus pallidus showing T1 concentric hypo- and hyper-intense signals and T2 central hyper-intense with peripheral hypo-intense signals, giving an eye of the tiger sign [Fig. 4c] and suggesting the diagnosis of HSS.

Case 5

A 17-year-old female presented with diminution of vision in BE since childhood with gradual worsening. She was unable to maintain balance for the past 2 years. She also gave a history of headache which was confined to the frontal and temporal region. The family history was non-contributory. The BCVA was 5/60 in BE. Anterior segment examination was unremarkable. Fundus examination revealed waxy pallor of the disc with attenuated arterioles in BE with pigmentary retinopathy. SD-OCT revealed foveal thinning with photo-receptor layer loss and retinal pigment epithelium (RPE) irregularity in BE [Fig. 5a]. The electroretinogram (ERG) showed an extinguished photopic and diminished scotopic response suggestive of cone-rod dystrophy [Fig. 5b]. Visual evoked potential (VEP) revealed prolonged latency and a reduced amplitude in BE, suggestive of bilateral axonal neuropathy. Polymerase chain reaction analysis revealed repeat CAG (cytosine, adenine, and guanine) nucleotide expansion, which confirmed the diagnosis of SCA 7. The patient was advised environmental modifications, speech therapy along with low vision aids, and a walker.

Discussion

KSS is a rare autosomal dominant, autosomal recessive, mitochondrial disorder with an incidence of 1–3/100,000. The failure to recognize this disease and refer to specialist centers is common.^[1] The classical triad of KSS is onset before 20 years of age, external ophthalmoplegia, and pigmentary retinopathy. It can be associated with cardiac conditions, mental retardation, limb weakness, seizures, hearing loss, short stature, and endocrinal disorders.^[1] In 1958, Kearns and Sayre were the first to report two cases having the triad.^[2]

Primary mitochondrial disorders of the retina are those in which the first pathogenic event is the inheritance or development of a mutation within the mitochondrial genome. These include maternally inherited diabetes and deafness, which may present as a pattern of macular dystrophy, and KSS, which presents as pigmentary retinopathy.^[3] Cases 1 and

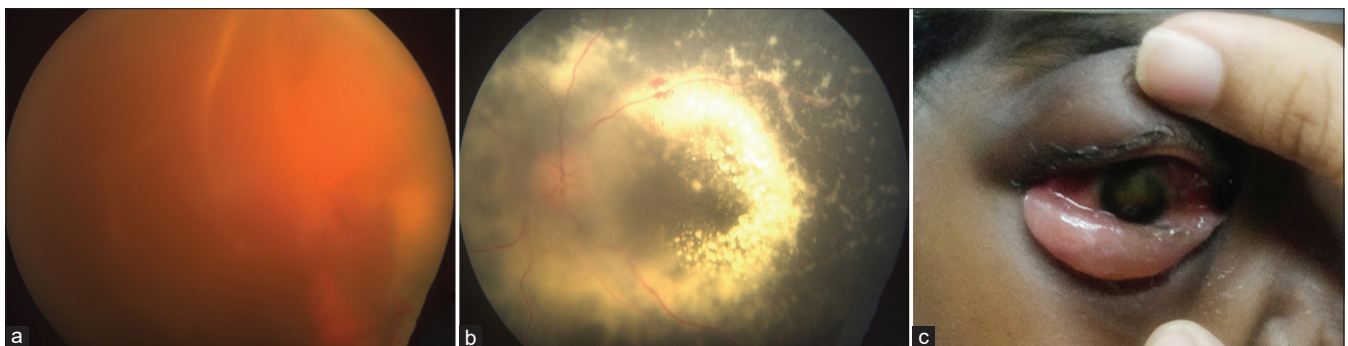


Figure 3: (a-c) (case 3) – Color fundus photograph of the RE revealing exudative retinal detachment (a) and LE showing extensive hard exudate clumping with exudative retinal detachment nasally (b). Follow-up external photograph of the RE revealing lid edema, proptosis, and conjunctival chemosis, suggestive of orbital cellulitis (c)

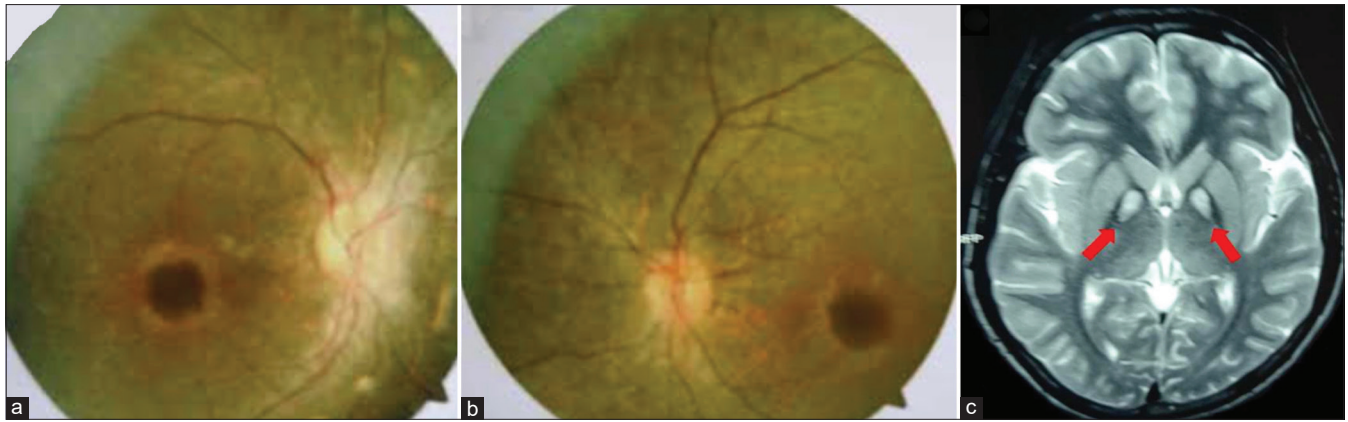


Figure 4: (a-c) Color fundus photograph of case 4 with HSS revealing pigmentary retinopathy in BE (a and b) MRI of the brain showing the “eye of the tiger” sign (red arrows) (c)

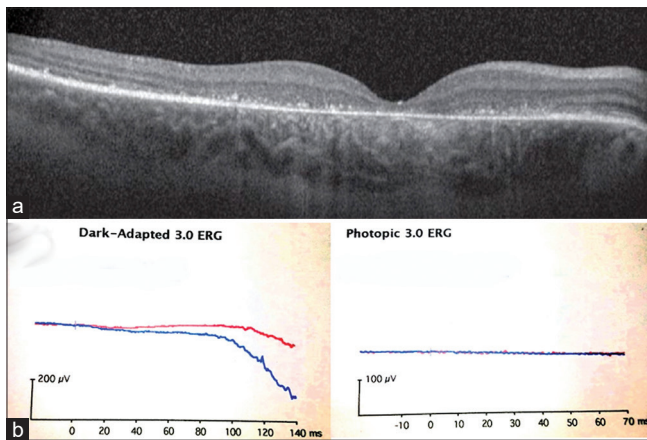


Figure 5: (a and b) SD-OCT of case 5 with SCA type 7 showing retinal thinning with the absence of photo-receptors (a) ERG of case 5 showing diminished scotopic and photopic responses (b)

2 were diagnosed with KSS based on the clinical features and hematological and imaging workup. The clinical course of the retinal findings in KSS is usually benign with patients having normal or near-normal vision unlike case 1 where the visual acuity was reduced, especially in the RE. Birtel *et al.*^[3] utilized the term mitochondrial retinopathy to describe the retinal changes in a variety of mitochondrial diseases and classified them into four types and reported that the KSS phenotype is a type 3 mitochondrial retinopathy; however, they did not describe any asymmetrical pattern of presentation. In case 1, MMI revealed significantly more widespread areas of RPE atrophy involving the fovea in the RE, whereas fovea was relatively spared in the LE. SD-OCT findings revealed extensive photo-receptor and RPE loss in the RE along with outer retinal tubulations in the RE, whereas photo-receptors were spared sub-foveal in the LE along with sparing of the RPE. OCTA also revealed extensive choriocapillaris loss under the macular and peri-papillary region in the RE, whereas choriocapillaris was relatively normal in the LE. In case 1, MMI features describe the pigmentary retinopathy in KSS, although seen in a gross asymmetrical pattern between BE, with the RE being extensively involved. The differences in retinopathy between BE could be because of the differences in heteroplasmy across the retina. Case 1 shows relatively new findings on MMI of retinal manifestations in

KSS as well as its rare presentation in an asymmetric pattern.

SLS is a rare autosomal recessive disorder with an incidence of 1/100000.^[4,5] Renal diseases often also involve the retina because the kidney and the retina develop at the same embryonic stage and share the same developmental pathways. The retinal lesions in the SLS are variable, ranging from severe Leber's amaurosis to a more typical RP.^[5,6] Ocular involvements in SLS also include nystagmus, amblyopia, Coats' disease, cataract, and keratoconus, depending on the gene variant.^[6] Khairil-Ridwan *et al.*^[5] reported the combination of endolaser photo-coagulation and external drainage of the sub-retinal fluid in a teenager with SLS presenting with unilateral retinal detachment, although the final visual acuity was poor in BE. Clarke *et al.*^[6] reported two pediatric cases with SLS. However, despite these treatments, BE finally had a poor visual prognosis. Regular ophthalmic examinations are warranted in patients with chronic kidney disease so that timely advice and treatment can be given before irreversible damage occurs. Case 3 highlights the various ophthalmic manifestations in a case of SLS.

HSS is a rare autosomal recessive disorder with a mutation in the gene for pantothenate kinase 2. It presents in the first 2 decades of life with progressive extra-pyramidal symptoms and with an average life span of 11.8 years after diagnosis.^[7] Extra-pyramidal features include dystonia, dysarthria, rigidity, and choreoathetosis. Cognitive impairment and psychiatric manifestation can also be present. Others features include tremors, dysphagia, seizures, and speech disturbances. Ocular manifestations include Kayser Fleisher rings, pigmentary retinopathy, and optic atrophy. 25% of patients have flecked the retina with bull's eye maculopathy.^[8] Classic disease has an early onset with predominantly extra-pyramidal features and cortico-spinal tract involvement. Loss of ambulation in 10–15 years and pigmentary retinopathy is always associated with the disease. The atypical form includes speech impairment and psychiatric issues with extra-pyramidal signs.^[9] The characteristic MRI imaging finding is known as the eye-of-the-tiger sign,^[10] which was seen in case 4. We report a case of HSS where the patient had an atypical form presenting with pigmentary retinopathy and speech impairment.

SCAs are autosomal dominant progressive neuro-degenerative and inherent disorders. They are characterized clinically by progressive loss of coordination in gait and limb movements.^[11]

SCA7 is caused by a poly-Q expansion in the protein ataxin-7 and is a rare autosomal dominant disease characterized by cerebellar ataxia and macular degeneration, which is progressive and rare.^[12-14] Atrophy of the spino-cerebellar pathways, pyramidal tracts, and motor nuclei in the brainstem and spinal cord along with cone-rod dystrophy of the retina and ataxin 7 immuno-reactive neuronal intra-nuclear inclusion bodies are the pathological changes of the disease.^[15]

In case 5, we carried out a thorough eye examination with the patient having visual symptoms associated with the onset of ataxic symptoms. The patient had a diminished visual acuity of 5/60 in BE. The disc showed waxy pallor with attenuated arteriolar attenuation. SD-OCT indicated that there was foveal thinning with photo-receptor layer loss. ERG revealed extinguished photopic and diminished scotopic response, which suggested cone-rod dystrophy. VEP revealed prolonged latency and a reduced amplitude, suggestive of bilateral axonal neuropathy.

The relation between the eye defects and symptoms of the motor system could suggest that both impairments follow the same progression, and it can be explained that degeneration mechanisms of SCA7 are the result of mutation located in the short arm of chromosome 3 with the polyglutamine tract of the encoded protein being considered responsible.^[16,17]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conclusion

To conclude, we describe multiple rare syndromes presenting with a variety of ophthalmic manifestations including retinopathies, which are common manifestations in these disorders and highlight the importance of retinal evaluation and support the diagnosis and rehabilitation of the patient.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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