

# Ophthalmologic Findings in Patients with Neuro-metabolic Disorders

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## Abstract

**Purpose:** We aimed to present the ophthalmic manifestations of neuro-metabolic disorders.

**Methods:** Patients who were diagnosed with neuro-metabolic disorders in the Neurology Department of Mofid Pediatric Hospital in Tehran, Iran, between 2004 and 2014 were included in this study. Disorders were confirmed using clinical findings, neuroimaging, laboratory data, and genomic analyses. All enrolled patients were assessed for ophthalmological abnormalities.

**Results:** A total of 213 patients with 34 different neuro-metabolic disorders were included. Ophthalmological abnormalities were observed in 33.5% of patients. Abnormal findings in the anterior segment included Kayser–Fleischer rings, congenital or secondary cataracts, and lens dislocation into the anterior chamber. Posterior segment (i.e., retina, vitreous body, and optic nerve) evaluation revealed retinitis pigmentosa, cherry-red spots, and optic atrophy. In addition, strabismus, nystagmus, and lack of fixation were noted during external examination.

**Conclusion:** Ophthalmological examination and assessment is essential in patients that may exhibit neuro-metabolic disorders.

**Keywords:** Cherry Red Spot; Lens Dislocation; Neuro-metabolic Disorders; Optic Atrophy; Pediatric; Retinitis Pigmentosa

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## INTRODUCTION

Neuro-metabolic disorders are caused by both neuronal and metabolic system involvement. The type and extent

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of evaluation for the chronic forms of these disorders depends on demographic information, including sex, age, underlying disorders, family history, and specific signs and symptoms.<sup>[1]</sup> Neuro-metabolic disorders, often caused by defects in enzymatic functions, are classified in different subgroups.<sup>[2-4]</sup> Patients with neuro-metabolic disorders might present with seizures, aciduria, developmental delays, and/or ophthalmological abnormalities.<sup>[5-8]</sup> Progressive external ophthalmoplegia has been mentioned as one of the symptoms in mitochondrial disorders

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(such as Kearns–Sayre syndrome).<sup>[9]</sup> Pigmentary degeneration of the retina may be observed in Hallervorden–Spatz syndrome.<sup>[10]</sup> Corneal clouding is a common manifestation in Hurler’s syndrome.<sup>[11]</sup> Retinitis pigmentosa and cataracts are the signs of Refsum disease.<sup>[12]</sup> Corneal clouding and cherry-red macula are among the most common clinical symptoms of GM1 gangliosidosis reported in 60% of these patients.<sup>[13]</sup> Optic nerve atrophy is one of the clinical features of Canavan disorder.<sup>[14]</sup> In this study, we present neuro-ophthalmologic findings of all neuro-metabolic cases referred to the Pediatric Neurology Research Center of Mofid Children’s Hospital, Tehran, Iran, within a 10-year period.

## METHODS

This retrospective study was performed on patients who were diagnosed with neuro-metabolic disorders in the Neurology Department of Mofid Children’s Hospital in Tehran, Iran, between March 2004 and May 2014. The diagnosis was based on clinical manifestations, neuroimaging findings, and laboratory assessments in a reference lab in Germany (Wagner Stibble laboratory, Hanover, Germany). Data including age, sex, past medical history, developmental status, general appearance, and clinical and neuroimaging findings were collected.

Diagnostic criteria of neuro-metabolic disorders were classified based on the type of disorder, such as enzymatic assessments for biotinidase deficiency, Sandhoff and Tay–Sachs diseases, metachromatic leukodystrophy (MLD), and galactosemia; acil carnitin profile assessment for lipid oxidation disorders; serum acil carnitin profile assessment and urine organic acid evaluation for organic acidemia; very long-chain fatty acid (VLCFA) assessment for paroxysmal disorders; genetic assessment for Pelizaeus–Merzbacher disease (PMD), PMD-like diseases, and neuronal ceroid lipofuscinosis (NCL). All patients underwent ophthalmological examination. Refraction was performed for all patients and if the patient’s condition was appropriate (mental status, cooperation, age), the best corrected visual acuity (BCVA) was documented. Abnormal ocular motilities, strabismus, nystagmus, abnormal head tilts and face turns, and eyelids abnormalities such as ptosis, were also documented. Anterior segments (cornea, anterior chamber, lens, and anterior vitreous body) were examined using slit lamp biomicroscopy, and fully dilated fundus examination using indirect ophthalmoscopy and slit lamp biomicroscopy was also performed in all patients to assess their retinas, vitreous bodies, and optic nerves. Institutional ethical approval for the conduct of this study was obtained from the Pediatric Neurology Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All parents signed a written consent form for

participation in the study. Data in this study were analyzed using SPSS software version 18. (SPSS Inc., Chicago, IL, USA).

## RESULTS

A total of 213 patients with 34 different disorders were included. They were classified into 7 subgroups: 1) organic acidemia and aminoacidopathy, 2) lipid oxidation disorders, 3) storage diseases, 4) urea cycle disorders, 5) progressive myoclonic epilepsy, 6) proxysomal disorders, and 7) leukodystrophy. The findings for the evaluated patients are summarized in Table 1. Among these patients, 45.7% were female and 54.3% were male. The average age of the patients at the time of diagnosis was 41 months. Of all patients, 71.4% were offspring of consanguineous marriages (57.4% of them were second-degree and 14% were third-degree); 23.5% of patients also presented a positive family history of similar diseases.

During developmental assessment, only 13% of patients exhibited normal development; 47.5% of patients showed developmental delay; 21% demonstrated developmental delay and regression; 18.5% of them presented with developmental regression.

Seventy-two patients of the total 213 patients exhibited ophthalmological abnormalities, including 34 cases with blurred vision. Ophthalmologic findings from external examination included ptosis (1 patient), nystagmus (8 patients), strabismus (11 patients), vertical gaze palsy (4 patients), and lack of fixation (12 patients). Cataracts (4 patients), Kayser–Fleischer ring (1 patient), and lens dislocation (3 patients) were the pathologic findings from anterior segment examinations. In fundusoscopic and posterior segment evaluation, pathologic findings included cherry-red spots (23 patients, including 18 patients with GM2 gangliosidosis disease), optic atrophy (4 patients), retinitis pigmentosa (2 patients with Zellweger syndrome), and ocular albinism (1 patient).

Ophthalmological abnormalities were observed in 33.5% of patients with the following distributions: 17.2% of cases with amino acidopathy; 78.4% of cases with storage disorders; 33.3% of cases with urea cycle disorders; 55.6% of cases with paroxysmal disorders; 9% of cases with fatty acid oxidation defects; 44.4% of cases with leukodystrophy; and 25% of cases with progressive myoclonic epilepsy [Table 2].

## DISCUSSION

Ophthalmological evaluation is warranted in patients with suspected neuro-metabolic disorders. One-third of our patients exhibited ophthalmological involvement. Some neuro-metabolic disorders have specific ophthalmic involvements that are important for diagnosis, such as blurred vision due to optic atrophy in patients with biotinidase deficiency. Biotinidase deficiency is

**Table 1. Summary of findings in evaluated patients**

Gender	Male: 54.3%	Female: 55.7%
Age (month)	41±46.1(Mean±SD)	Min: 0.5 Max: 276
Consanguinity of marriage	Positive :71.4%,	Negative: 28.6%
Family history of same disease	Positive :23.5%,	Negative: 76.5%
Developmental status	Abnormal :87%	Normal: 13%
Ophthalmologic problem	Positive 32.9% (loss of vision; strabismus; nystagmus; retinitis pigmentosa; lack of fixation; Kayser–Fleischer ring; blurred vision; optic atrophy; lens dislocation; secondary cataract and cherry red spot)	Normal: 67.1%
Convulsion	Positive:55.5%	Normal: 45.5%
EEG Findings	Abnormal:20.8%	Normal: 79.2%
Brain MRI findings	Abnormal:64%	Normal: 36%

Min, minimum; Max, maximum; SD, standard deviation; EEG, electroencephalography; MRI, magnetic resonance imaging

**Table 2. Ophthalmologic findings in evaluated cases with neuro-metabolic disorders**

Neuro-metabolic disorders	Ophthalmologic abnormalities	Percentage per disorders
Amino Acidopathy (58 patients)	Strabismus (3 patients, 5.17%) Nystagmus (2 patients, 3.44%) Lens dislocation (3 patients, 5.17%) Ocular albinism (1 patient, 1.72%) Blurred vision (8 patients, 13.79%)	17.2%
Storage disorders (36 patients)	Lack of fixation (4 patients, 11.11%) Blurred vision (9 patients, 25%) Strabismus (4 patients, 11.11%) Nystagmus (3 patients, 8.33%) Cherry red spot (16 patients, 44.44%) Cataract (4 patients, 11.11%)	78.4%
Urea Cycle disorders (12 patients)	Strabismus (4 patients, 33.33%) Nystagmus (3 patients, 25%)	33.3%
Paroxysmal disorders (11 patients)	Blurred vision (6 patients, 54.54%) Optic atrophy (4 patients, 36.36%)	55.6%
Fatty Acid Oxidation defect (34 patients)	Secondary cataract (1 patients, 2.9%) Blurred vision (5 patients, 14.70%)	9%
Leukodystrophy (30 patients)	Retinitis pigmentosa (2 patients, 6.66%) Lack of fixation (8 patients, 22.22%) Cherry red spot (7 patients, 23.33%)	44.4%
Progressive Myoclonic Epilepsia (32 patients)	Vertical gaze palsy (4 patients, 12.5%) Blurred vision (6 patients, 18.75%)	25%

an autosomal recessive disorder with neurological involvement and optic atrophy.<sup>[15,16]</sup> Visual loss owing to optic atrophy has been reported in some studies.<sup>[17-19]</sup> Hayati et al have shown that 85.7% of their recruited patients with biotinidase deficiency presented with optic atrophy and 71.4% of them had poor visual outcomes.<sup>[16]</sup> In this study, 37% of patients with biotinidase deficiency had ophthalmological involvement, including loss of vision, strabismus, or nystagmus. It is pivotal for both pediatricians and ophthalmologists to be aware of possible biotinidase deficiency in patients who present with visual loss.

Retinitis pigmentosa was only found in patients with Zellweger syndrome, which is caused by an inherited defect in the Peroxisomal Biogenesis Factor (PEX) gene. This deficiency can also cause loss of vision and hearing.<sup>[20]</sup>

This bi-functional enzyme deficiency disorder is associated with retinal involvement.<sup>[21]</sup> In this study, 3 out of 5 patients with this disorder had retinitis pigmentosa and lack of fixation as their ophthalmological manifestation.

Wilson's disease is caused by a deficiency in P-type Cu (2+)-ATPase (Atp7b).<sup>[22]</sup> Cataracts and secondary glaucoma are observed in patients with Wilson's disease.<sup>[23,24]</sup> Kaiser–Fleischer rings are the most common characteristic findings of Wilson's disease with neurological involvement.<sup>[25]</sup> In the current study, all the patients with Wilson's disease exhibited Kaiser–Fleischer rings. Nystagmus was found in patients with PMD and PMD-like disorders.<sup>[26]</sup> The patients in our study with PMD and PMD-like disorders presented with infantile nystagmus.

Blurred vision, optic atrophy, and white matter involvement were found in Canavan disease, MLD, and

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adrenoleukodystrophy (ALD).<sup>[1,14]</sup> In this study, 35% of patients with Canavan disease exhibited blurred vision and optic atrophy.

Homocystinuria is an autosomal recessive disorder that is caused by a deficiency in cystathionine-beta-synthetase. Ophthalmic complications include optic atrophy, secondary glaucoma, cataracts, and retinal detachment.<sup>[27]</sup> In this study, 35% of patients with homocystinuria exhibited lens dislocation and secondary cataracts.

GM2 gangliosidosis is classified into two groups: Sandhoff disease, which may present with developmental regression within the first 6 months of life, and Tay–Sachs disease, which is caused by an accumulation of gangliosides in the retina and brain.<sup>[28,29]</sup> Patients with GM2 gangliosidosis may develop cherry-red spots due to an accumulation of GM2 gangliosides in the ganglion cells of the retina, resulting in retinal posterior pole thickness and loss of transparency.<sup>[30]</sup> In the current study, 90% of patients with GM2 gangliosidosis (Sandhoff and Tay–Sachs diseases) exhibited cherry-red spots.

In this study, 66% of patients with Niemann–Pick type C disease exhibited vertical gaze palsy. Abnormal vertical optokinetic nystagmus may be observed in patients with Niemann–Pick type C disease.<sup>[31]</sup> All patients with NCL presented with optic atrophy in this study. This disorder is very important to consider for ophthalmological examination. NCL may present with a dramatic loss of vision, blindness, or optic atrophy.<sup>[32]</sup> Furthermore, 75% of patients with Chiari malformation type 1 (CM1) disease exhibited optic atrophy.

In conclusion, we suggest that the diagnosis of neuro-metabolic disorders may be facilitated by the detection of ophthalmologic abnormalities. This would allow for early intervention and enhance prenatal diagnosis of the disease in future offspring. Early diagnosis can help us in preventing and inhibiting the progression of signs and symptoms in selected neuro-metabolic disorders through appropriate treatment. We suggest conducting ophthalmic examinations in all patients suspected to harbor neuro-metabolic disorders.

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## Conflicts of Interest

There are no conflicts of interest.

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