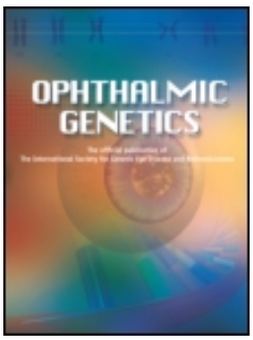

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CASE REPORT

Neuro-ophthalmologic findings in humans with quadrupedal locomotion

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ABSTRACT

Purpose: To report the neuro-ophthalmologic findings in four patients from the same family with cerebellar ataxia, mental retardation, and dysequilibrium syndrome (CAMRQ)2 associated with quadrupedal locomotion.

Method: A case series.

Results: All four patients carry the private missense mutation, *WDR81* p.P856L. The brain Magnetic Resonance Imaging (MRI) of these patients revealed morphological abnormalities including mild hypoplasia of the corpus callosum, and atrophy of superior, middle, and inferior peduncles of the cerebellum. All patients had down-beat nystagmus, while two male patients additionally had bilateral temporal disc pallor along with ring-shaped macular atrophy.

Conclusions: The neuro-ophthalmic examination in CAMRQ2 revealed downbeat nystagmus in all patients, and temporal disc pallor and macular atrophy in two patients. It remains to be determined whether these findings are consistent in other forms of CAMRQ with mutations in *VLDLR* or *CA8*.

KEYWORDS: Cerebellar ataxia, mental retardation, dysequilibrium syndrome (CAMRQ), quadrupedal locomotion, neuro-ophthalmologic findings

INTRODUCTION

Cerebellar ataxia, mental retardation, and dysequilibrium syndrome (CAMRQ) is a genetically heterogenous autosomal recessive disorder which was first described by Schurig in 1981.[1] In 2005 Tan first described a group of patients with CAMRQ associated with quadrupedal gait.[2] The CAMRQ is characterized by congenital onset of cerebellar ataxia, disturbed equilibrium, and mental retardation, associated with cerebellar hypoplasia. Three different genes including the *VLDLR* gene encoding the very low density lipoprotein receptor (CAMRQ1 – MIM 224050), *WDR81* gene encoding WD repeat domain 81 (CAMRQ2 – MIM 610185), and *CA8* gene encoding carbonic anhydrase VIII (CAMRQ3 – MIM 613227) have been identified to harbor the causative mutations that lead to the phenotype of the CAMRQ.[2–5]

The quadrupedal gait is walking on all four extremities which occurs as a developmental regression with absence of the higher control mechanisms for asymmetric lateral balance during bipedal walking (Fig. 1).[2] The subjects with quadrupedal gait preferred quadrupedal walking because of the difficulties maintaining a dynamic-asymmetric lateral balance and initiation of the first step during standing. They begin to move by crawling at the end of their first year but never learn to walk bipedally. They are able to stand upright without a support. However when they try to walk upright, they exhibit strong ataxia and return to the palmigrade walking position.

In this report, we present the neuro-ophthalmologic findings of four patients from the same family with CAMRQ2, of whom three were quadrupedal and one was bipedal. These patients carry the private missense mutation, WDR81 p.P856L.[5]

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All patients underwent complete neurologic and ophthalmologic examination including visual acuity, color vision, pupillary light reflex, slit-lamp, ocular motility and dilated fundoscopic examinations. To our knowledge the current report is the first one presenting the neuro-ophthalmologic findings in the CAMRQ2.

CASES

Case 1

A 34-year-old male had quadrupedal gait (Fig. 1), severe mental retardation, and ataxia. His visual acuity and color vision were not possible to check because of the lack of cooperation. Pupils were equal, round, and reactive to light without evidence of relative afferent pupillary defect. Slit-lamp examination revealed normal findings for both eyes except some anterior peripheral cortical opacities in the left lens. The eye movements were full in all positions of gaze. A downbeat nystagmus was observed in primary gaze and persisted in all other positions of the gaze. The dilated fundoscopic examination revealed bilateral temporal disc pallor along with ring-shaped macular atrophy.

Case 2

A 30-year-old female had quadrupedal gait, mental retardation, ataxia, dysmetria, and intention tremor. The visual acuity for both eyes was counting fingers from 3 meters. The Snellen acuity chart could not be used to evaluate vision because of the poor compliance of the patient. Color vision was not able to checked. Pupils were equal, round, and reactive to light with no evidence of relative afferent pupillary defect. Biomicroscopic examination revealed no abnormality in both eyes. She had full ductions in all positions of gaze. A downbeat nystagmus in the primary position and downgaze which increased in velocity on gazes to the left and right was present. The dilated fundoscopic examination revealed normal findings in both eyes.

FIGURE 1 The quadrupedal gait of case 1.

Case 3

A 40-year-old male had bipedal ataxic gait, mental retardation, bilateral sensorineural hearing loss, mild dysmetria, and intentional tremor. The visual acuity for both eyes was counting fingers from 3 meters. The Snellen chart could not be used to evaluate the visual acuity and color vision could not be tested because of the poor compliance of the patient. Pupils were equal, round, and reactive to light without evidence of relative afferent pupillary defect. Biomicroscopic examination revealed normal for both eyes. The eyes had full ductions. A downbeat nystagmus in the primary position which increased in velocity on downward gaze was detected. Similar to case 1, dilated fundoscopic examination revealed bilateral temporal disc pallor along with ring-shaped macular atrophy (Fig. 2).

Case 4

A 24-year-old female had quadrupedal gait and mental retardation. The visual acuity and color vision could not be examined because of her poor cooperation. Pupils were equal, round, and reactive to light with no evidence of relative afferent pupillary defect. Biomicroscopic examination was normal. There was no limitation of eye movements. A downbeat nystagmus was present in the primary position and persisted in right, left, and upgaze positions, but not in downgaze.

The dilated fundoscopic examination revealed no abnormality.

Table 1 summarizes the demographic findings, the gene mapping, brain magnetic resonance ımaging (MRI) abnormalities, and major neurologic and ophthalmologic findings of all four cases.

DISCUSSION

Quadrupedal palm-gait with cerebellar and vermian hypoplasia and limited cognitive abilities in humans was first reported in 2005,[2] and since then it has been documented in a number of families from around the

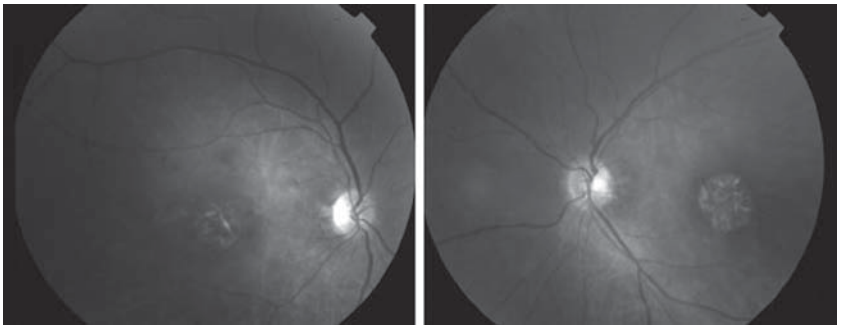

FİGURE 2 Bilateral temporal disc pallor and ring-shaped macular atrophy, and bilateral intorsion of the globes seen in case 3.

TABLE 1 The demographic findings, the gene mapping, brain magnetic resonance ımaging (MRI), and major neurologic and ophthalmologic findings of all four cases.

Case number	Gender	Age (years)	Gene mapping	Neurologic findings	Ocular findings	Brain MRI findings
1	Male	34	WDR81 p.P856L on chromosome 17p13.1-13.3	Severe mental retardation, unable to talk, quadrupedal gait, severe ataxia	Downbeat nystagmus, bilateral temporal disc pallor, bilateral ring shaped macular atrophy anterior peripheral cortical opacities in the left lens	Atrophy of the superior, middle, and inferior peduncles of the cerebellum
2	Female	30	WDR81 p.P856L on chromosome 17p13.1-13.3	Mental retardation, can communicate only with her sister, quadrupedal gait, ataxia, dysmetria, intention tremor	Downbeat nystagmus	Atrophy of the superior, middle, and inferior peduncles of the cerebellum
3	Male	40	WDR81 p.P856L on chromosome 17p13.1-13.3	Mental retardation, able to talk, bilateral sensorineural hearing loss, bipedal, ataxic gait, mild dysmetria, intentional tremor	Downbeat nystagmus, bilateral temporal disc pallor, bilateral ring shaped macular atrophy	Atrophy of the superior, middle, and inferior peduncles of the cerebellum
4	Female	24	WDR81 p.P856L on chromosome 17p13.1-13.3	Mental retardation, can communicate only with her sister, quadrupedal gait, not cooperative for finger to nose test	Downbeat nystagmus	Atrophy of the superior, middle, and inferior peduncles of the cerebellum

world. Severe mental retardation, low-level conscious experience, speech disturbance, truncal ataxia with or without quadrupedal locomotion are observed in the affected individuals.[1–7]

In this report we investigated the neuro-ophthalmic findings of four patients from the same family with CAMRQ2 that harbour the WDR81 p.P856L mutation. The *WDR81* gene on chromosome17p13.1-13.3 is predicted to encode for a transmembrane protein highly expressed in the cerebellum and corpus callosum, in particular in the Purkinje cell layer of the cerebellum.[5] The function of this gene is not known and further studies should be done in order to reveal the mechanistic insights of cerebellar development and quadrupedal gait in humans.

The neuro-ophthalmic examination demonstrated that a down-beat nystagmus, an ocular motor sign typical for vestibulo-cerebellar lesions was present in all examined patients. Downbeat nystagmus is a vertical pursuit disorder and characterized by slow upward drifts and fast downward phases.[8] The cerebellar nodulus and uvula play an important role in the control of the vertical pursuit. In cerebellar disease the downward pursuit is substantially reduced while the upward pursuit is relatively spared, causing an asymmetry in vertical pursuit. This asymmetry may lead to spontaneous upward drift that causes downbeat nystagmus.[8,9] Downbeat nystagmus has been demonstrated in animals with cerebellar nodulus and uvula lesions.[10] As previously reported, the neuroimaging techniques such as diffusion weighted imaging and fiber tractography of these reported patients' brains revealed morphological abnormalities in the cerebellum and corpus callosum, in particular atrophy of superior, middle, and inferior peduncles of the cerebellum.[5] These findings explain the presence of the downbeat nystagmus in our patients.

The two male patients (Cases 1 and 3) had temporal disc pallor, and ring shaped macular chorioretinal atrophy, while females had normal fundus findings. Although case 1 was quadrupedal, and case 3 was bipedal they had the same optic disc and macular findings which may be specific manifestations of a kind of fundus dystrophia.

In conclusion, the neuro-ophthalmic examination in CAMRQ2 revealed downbeat nystagmus in all four patients, and temporal disc pallor and macular atrophy in two males. It needs to be confirmed whether these

findings are consistent in other patients with the same disorder with mutations in *VLDLR* or *CA8*.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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