BMJ Case Reports

Unusual association of diseases/symptoms

Is blinking of the eyes affected in extrapyramidal disorders? An interesting observation in a patient with Wilson disease

Rajesh Verma, Rakesh Lalla, Tushar B Patil

Department of Neurology, Chhatrapati Shahuji Maharaj Medical University, Lucknow, Uttar Pradesh, India

Correspondence to Professor Rajesh Verma, drrajeshverma32@yahoo.com

Summary

Blinking of eye is a routine human activity which seldom attracts any attention of clinicians in health and disease. There is experimental evidence that blink rate is affected in extrapyramidal disorders affecting the balance of these neurotransmitters. However, no observations regarding blink rate in Wilson disease (WD) have been reported previously. We report a patient of WD with an increased spontaneous blink rate. A 24-year-old lady presented complaining of tremulousness of both upper limbs and head for 2 years, dysphagia and difficulty in speaking for 1.5 years and abnormal behaviour for last 1 year. We observed that her blink rate at rest was 32/min. Serum ceruloplasmin level was low (0.08 g/l). The patient was started on therapy with D-penicillamine, zinc sulphate, levodopa-carbidopa and trihexiphenidyl. At 1-month follow-up, patient's tremors were markedly decreased and blink rate at rest was decreased to 12/min.

BACKGROUND

Blinking of eye is a routine human activity which seldom attracts any attention of clinicians in health and disease. Blink rate is controlled by a complex neuronal circuit comprising pontine paramedian reticular formation (PPRF), substantia nigra, superior colliculus, cerebellum, occipital cortex and probably thalamus. (a) It is affected by many factors such as concentration, reading, speaking, rest, voluntary suppression and local ocular pathology. Observational studies also point towards variability in blinking pattern in various normal individuals. Experimental data show that the neurochemical control of blinking is effected through, dopaminergic, cholinergic and gamma-aminobutyric acid (GABA)-ergic neurons.[1] There is experimental evidence that blink rate is affected in extrapyramidal disorders affecting the balance of these neurotransmitters. However, no observations regarding blink rate in Wilson disease (WD) have been reported previously. We report a patient of WD with an increased spontaneous blink rate.

CASE PRESENTATION

A 24-year-old lady was brought by her husband with complains of tremulousness of both upper limbs and head for 2 years, dysphagia and difficulty in speaking for 1.5 years and abnormal behaviour for last 1 year. She also had history of two episodes of tonic posturing of all limbs, lasting for a few minutes, 2 days prior to hospitalisation. She did not have weakness in any of the limbs, diminution of vision or urinary or bowel complains. Her family history was non-contributory.

Clinical examination revealed a conscious and oriented lady with intact higher mental functions. Her cranial nerve examination was normal. However, we observed that her blink rate at rest was 32/minute. Nutrition, tone, power and deep tendon reflexes were normal in all four limbs. Planters were bilateral flexors. She had postural tremors in the 'wing beating' position. Sensory and cerebellar examination was normal.

INVESTIGATIONS

Routine haematological and biochemical parameters of the patient were within normal limits. Serum bilirubin 0.7 mg/dl, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and serum alkaline phosphatise levels were 36, 27 and 114 IU/l, respectively. Serum protein level and albumin levels were 6.5 and 4 g/dl, respectively. The patient's international normalised ratio (INR) was1.46. Serum ceruloplasmin level was 0.08 g/l (normal range: 0.20–0.60 g/l). Twenty-four hours urinary copper excretion was 46.9 μg (normal <60 μg/24 h).The slit lamp study of both eyes demonstrated presence of Kayser-Fleischer ring (KF ring; figure 1). Ultrasonography of abdomen showed coarse hepatic echotexture with moderate splenomegaly

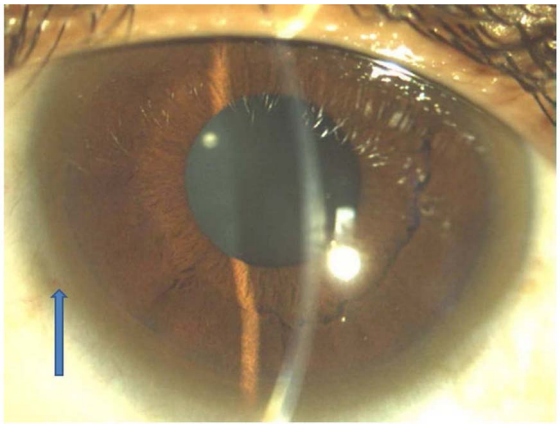

Figure 1 The slit lamp examination of the eye demonstrated Kayser-Fleischer ring (KF ring).

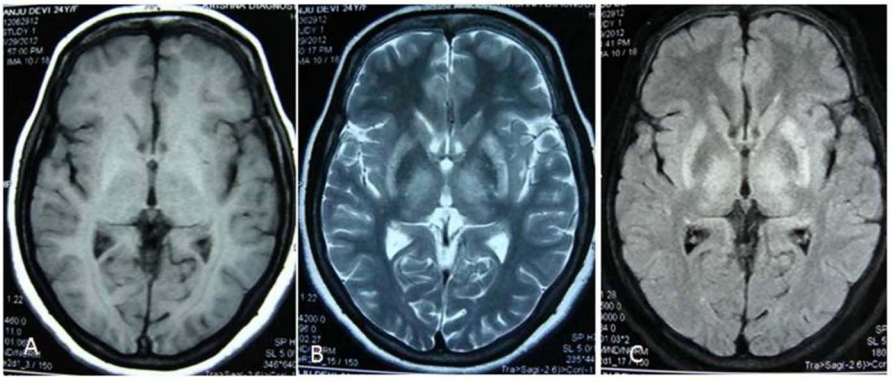

Figure 2 Axial MRI brain (A) T1-weighted image shows isointense signal in both caudate nuclei suggestive atrophy and necrosis of caudate, (B) and (C) T2-weighted and fluid attenuated inversion recovery images, respectively, show hyperintense signal bilateral caudate, putamen and thalamus typical of Wilson disease.

(15.1 cm) without any free fluid. Electrophysiological evaluation of bilateral blink reflex showed normal latencies. MRI of the brain revealed atrophy of caudate with cystic necrosis (isointense signal to cerebrospinal fluid) on T1-weighted image (figure 2A). Hyperintense signal was seen in bilateral caudate, putamen and thalamus on T2-weighted as well as fluid attenuated inversion recovery (FLAIR) (figure 2B,C) and hyperinstensity on T2-weighted images involving bilateral substantia nigra, cerebral peduncles and red nuclei (figure 3A,B). Thus, a diagnosis of WD was made on the basis of clinical presentation, reduced serum ceruloplasmin, the presence of KF ring and typical neuroimaging findings.

TREATMENT

Patient was started on chelating therapy with D-penicillamine 250 mg twice daily and zinc sulphate 50 mg thrice daily. Levodopa-carbidopa (110 mg TDS) and trihexiphenidyl (2 mg thrice daily) were started for extrapyramidal features.

OUTCOME AND FOLLOW-UP

At 1-month follow-up, the patient's tremors were markedly decreased. It was also observed that her blink rate at rest was decreased to 12/min.

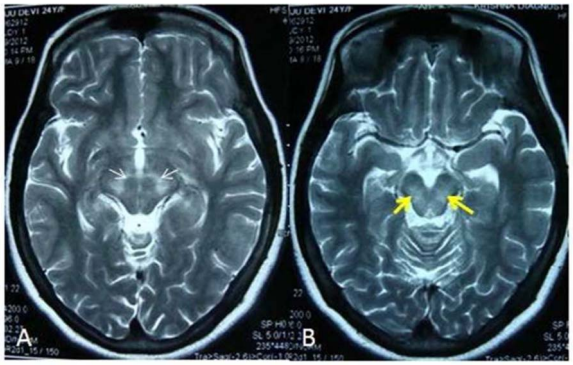

Figure 3 T2-weighted axial MRI brain shows (A) hyperintensity in bilateral cerebral pedunucles and red nuclei, (B) hyperintensity in the midbrain involving substantia nigra (yellow arrows).

DISCUSSION

'Blinking of eye' an extremely simple action performed by all of us without a slightest imagination about how complex its neuronal control may be. Blinking of the eye is unique and multidimensional; it is a protective reflex action that protects eyes from injury, its involuntary as well as undervoluntary control. It is mediated by neuronal integration of trigeminal, facial and oculomotor nerves which are continuously modulated by inputs from caudate, deep nuclei of cerebellum, cerebellar and cerebral cortex. Physiologically, blinking rate can increase due to local irritation of eye, age, sex (females have higher blink rate than males), conversation, mentally active tasks like calculations, anxiety, fatigue, etc whereas decreased blink rate is seen while reading, heightened alertness.[2–4]

The neurological manifestations of WD are caused due to excessive copper deposition in the brain. The diversity and presence of subtle signs and symptoms of WD especially in early course of disease poses a great diagnostic challenge. The disease commonly manifests in the second to third decade. The neurological presentation is more common in older individuals. The neurological abnormalities are classified as (1) akinetic rigid syndrome presents with parkinsonism, (2) pseudosclerosis dominated by tremor, (3) ataxic and (4) dystonic syndrome. WD should be suspected in all young patients with subtle signs like tremors, clumsiness, change in hand writing, facial grimacing, blepharospasm, drooling, dysphagia, dysarthria, dystonia (focal, multifocal, generalised and bilateral foot) and recent onset behavioural disturbances may be the initial presentation prior to development of florid signs.[5 6]

The cystic necrosis of both lenticular nuclei seems to be the most common abnormality; however other brain structures like putamen, caudate, thalamus, subthalamus, red nucleus, cerebral cortex involvement in the form of atrophy or degeneration may be seen. Cerebellar atrophy involving superior vermis and dentate nucleus have also been seen in WD.[7] PET studies using ^{18}F-6-fluorodopa was demonstrated low 6-FD uptake suggesting that parkinsonism in WD may be due to damage to dopaminergic nigrostriatal pathway as well as non-dopaminergic neuronal damage in the striatum.[8]

Dopamine is the neurotransmitter implicated in the regulation of blinking rate. Blinking rate is thus regarded

BMJ Case Reports 2012; doi:10.1136/bcr-2012-007367

as the measure of central dopaminergic reserve. The other neurotransmitters like GABA, glutamine, endogenous cannabinoids also modulate the release of dopamine and thereby affecting the blink rate. Modulation of D1 and D2 dopamine receptors by using dopamine agonist and antagonist can increase or decrease the blink rate, respectively. However dopamine receptor blockers may increase postsynaptic sensitivity to dopamine and thus lower the threshold for excitability of blink reflex.[9] Spontaneous blinking seems to arise from the activity of an endogenous blink generator, and spinal trigeminal complex is essential for its functioning. Depletion of dopamine increases trigeminal reflex excitability and amplitude. Animal models of parkinsonism have shown inhibitory GABAergic input to superior colliculus from straitum increases blink excitability. Hence, this can explain the basis of reduction in spontaneous blink by increasing the dopamine levels.[10 11]

In our patient, the increase in blinking rate was probably due to depletion of nigrostriatial dopamine which led to hyperexcitability of blink reflex. This increased blinking subsided after levodopa supplementation.

Learning points

- Wilson disease can have a varied clinical presentation with a combination of extrapyramidal and pyramidal features with neuropsychiatric manifestations.
- Blink rate can be affected in diseases involving extrapyramidal system such as Wilson disease.
- Blink rate is a simple clinical observation which may yield information about the underlying neurological disorder.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Karson CN.** Blinking. *Bull Soc Belge Ophtalmol* 1989;**237**:443–57.
2. **Karson CN.** Physiology of normal and abnormal blinking. *Adv Neurol* 1988;**49**:25–37.
3. **Bentivoglio AR,** Bressman SB, Cassetta E, *et al*. Analysis of blink rate patterns in normal subjects. *Mov Disord* 1997;**12**:1028–34.
4. **Karson CN,** Berman KF, Donnelly EF, *et al*. Speaking, thinking, and blinking. *Psychiatry Res* 1981;**5**:243–6.
5. **Svetel M,** Kozic D, Stefanova E, *et al*. Dystonia in Wilson's disease. *Mov Disord* 2001;**16**:719–23.
6. **Rathbun JK.** Neuropsychological aspects of Wilson's disease. *Int J Neurosci* 1996;**85**:221–9.
7. **Lewit P,** Pfeiffer R. Neurologic aspects of Wilson's disease: clinical manifestations and treatment considerations. In: Jankovic J, Tolosa E, eds. *Parkinson's disease & movement disorders*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:255–70.
8. **Snow BJ,** Bhatt M, Martin WR, *et al*. The nigrostriatal dopaminergic pathway in Wilson's disease studied with positron emission tomography. *J Neurol Neurosurg Psychiatry* 1991;**54**:12–17.
9. **Chan KKS,** Hui CLM, Lam MML, *et al*. A three-year prospective study of spontaneous eye-blink rate in first-episode schizophrenia: relationship with relapse and neurocognitive function. *East Asian Arch Psychiatry* 2010;**20**:174–9.
10. **Naase T,** Doughty MJ, Button NF. An assessment of the pattern of spontaneous eyeblink activity under the influence of topical ocular anaesthesia. *Graefes Arch Clin Exp Ophthalmol* 2005;**243**:306–12.
11. **Basso MA,** Powers AS, Evinger C. An explanation for reflex blink hyperexcitability in Parkinson's disease. I. Superior colliculus. *J Neurosci* 1996;**16**:7308–17.