

CRANIAL NERVES III, IV, AND VI: Oculomotor Function

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ABSTRACT

Motor activity affecting the direction of gaze, the position of the eyelids, and the size of the pupils are served by cranial nerves III, IV, and VI. Unusual oculomotor activity is often encountered in psychiatric patients and can be quite informative. Evaluation techniques include casual observation and simple tests that require no equipment in addition to the sophisticated methods used in specialty clinics and research labs. This article reviews pupil size, extraocular movements, nystagmus, lid retraction, lid lag, and ptosis. Beyond screening for diseases and localizing lesions, these tests yield useful information about the individual's higher cortical function, extrapyramidal motor functioning, and toxic/pharmacologic state.

GENERAL THOUGHTS

The general appearance of the eyes often conveys impressions about physical and mental condition. As seen most often in Victorian fiction, close observation of the eyes can reveal much about the mental state of healthy adults. We tend to associate sunken eyes, prominent folds beneath the eyes, discoloration beneath the eyes, and conjunctival injection with distress and fatigue. Eyes that are “glazed” (appearing to be unfocused) or reddish (due to conjunctival



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injection) elicit suspicions of fatigue and/or the use of intoxicating substances.

Spontaneous eye movements also have conventionally accepted implications. A lack of direct eye contact is taken to indicate a lack of confidence, authenticity, or interest; excessive eye contact can be taken as intimidating. Frequent lateral gazes (“shifty eyes”) sometimes implies anxiety or deception, but also may be assumed to reflect hypervigilance, paranoia, or hallucination. Because these features of the eyes can have so many causes, it is more useful to start with specific observations (e.g., frequent, rapid, spontaneous, lateral eye movements) rather than an inference (e.g., appears to be responding to internal stimuli) and then consider explanations.

Cranial nerves III (CNIII) (oculomotor), IV (trochlear), and VI (abducens) control the position of the eyeballs; CNIII influences the position of the eyelids and the size of the pupils. In addition to their value in localizing lesions, these three oculomotor nerves (sensory function is limited to proprioception) can reveal subtle changes in general skeletal and smooth muscle activity. For example, even minor weakness in one extraocular muscle can cause diplopia, and the eyelids reveal even mild variations in the activity of skeletal or smooth muscle.^{1,2} Motor activity controlling the direction of gaze, the elevation of the eyelids, and the size of the pupils also reflect higher cortical activity, and are sensitive to drug effects. As such, they are informative in common psychiatric conditions.

RELEVANT ANATOMY AND PHYSIOLOGY

Pupils. As discussed in the previous article of this series, light energy is transduced into neural activity in the retina, courses through the optic nerve (CNII), through the optic chiasm (where the nasal retinal projections, containing information from the

lateral visual fields, cross over), and then the optic tract (containing all information from the opposite visual hemifield).

The optic tract synapses in the pretectal nucleus, which projects equally to the Edinger-Westphal nucleus (part of CNIII) on both sides. The Edinger-Westphal nucleus sends efferent projections through CNIII to the ciliary ganglion, then to the pupil. Because projections from the pretectal to the Edinger-Westphal nuclei are bilateral, the pupils should respond about equally to light shined on either eye. Even a blind eye should constrict in response to light shined on the other eye. Unequal pupils (anisocoria) are due to the efferent (motor) system, which includes CNIII, somatic and parasympathetic components, sympathetic nerves originating in the cervical spine, and the smooth muscle of the iris.^{1,2}

Extraocular muscles. There are six extraocular muscles: four rectus muscles (superior, inferior, lateral, medial) and two oblique (superior and inferior). The oculomotor nerve (CNIII) innervates all but two of these, ipsilaterally. Partial lesions of CNIII are rare, so a lesion of the nucleus or nerve will result in a unilateral failure of almost all eye movements (as well as dilated pupil and ptosis). The nucleus is in the midbrain. The trochlear nerve (CNIV), also originating in midbrain, innervates the contralateral superior oblique, enabling the eye to point down while it is pointed medially. Lesions are rare, causing vertical diplopia and a compensatory tilt of the head that could be mistaken for dystonia. The abducens nerve (CNVI) originates in the pons, thus travelling farther to its destination (the lateral rectus muscle) than the others. Perhaps because of this, isolated lesions of CNVI, manifested by ipsilateral loss of lateral gaze (and inward deviation or esotropia at rest), are more common than of the others. The median longitudinal fasciculus links these nuclei, enabling coordination of the three

nuclei. Influencing the nuclei are widespread, higher (supranuclear) systems.^{1,2}

There are several anatomically distinguishable types of eye movement.^{3,4} Saccades are high-velocity movements used for visual search. They are elicited by having the patient rapidly shift gaze between two targets. Burst neurons, which activate saccades, are in the pons and the midbrain. Omnipause neurons, which inhibit the burst neurons, are in the pons. These brainstem systems are in turn controlled by the superior colliculus and frontal eye fields. Saccades are the most vulnerable to damage to the supranuclear systems.

In the vestibulo-ocular reflex, brief, rapid head movements provoke rapid compensatory eye movements. It is elicited at the bedside with the head impulse test. This is a simple circuit involving the vestibular receptors, the vestibular nucleus, and the three oculomotor nuclei (III, IV, and VI). It is free of influence from outside the brainstem, which is why a normal head impulse test supports the diagnosis of a supranuclear disorder.

The optokinetic response consists of slow tracking pursuit movements and quick resetting saccades. As there are now doubts about the validity of bedside assessments, it is probably best left to specialists. Retinal responses to large moving fields activate cells groups in the diencephalon and midbrain and generate the optokinetic response by influencing the vestibulo-ocular circuit.

Smooth pursuit is a low-velocity tracking activity. It is elicited at the bedside by asking the patient to follow a slowly moving target. This involves a complex circuit: Dorsal stream signals proceed from the diencephalon’s lateral geniculate nucleus to occipital and posterior parietal cortex. Posterior parietal output to the pons is relayed to cerebellum, which projects to the oculomotor nuclei. The frontal eye fields also contribute. Smooth

pursuit is famously impaired in schizophrenia, as well as in mood disorders.⁵

In vergence movements, the eyes move toward each other (convergence) or away from each other (divergence). It can be tested by having the patient continue tracking a target to a near midline position. Vergence movements require nuclei in midbrain and diencephalon, which receive visual input and relay to the oculomotor nuclei.

Gaze fixation “freezes” the gaze in a new position after a saccade. It depends on midbrain and medullary nuclei, which interact with vestibular and cerebellar centers and the frontal eye fields.

Eyelids. CNIII innervates the levator palpebrae superioris (skeletal) muscle, and sympathetic nerves innervate tarsal (smooth) muscles in both upper and lower lids. Thus the width of the eye opening is under both voluntary and autonomic control.^{1,2} Blinking, either spontaneously or in response to a stimulus, is affected by the orbicularis oculi, innervated by CNVII, and will be covered in the next article of this series.

SIGNS AND SYMPTOMS

Pupils. The size of pupils decreases from childhood to senescence. From moment to moment, normal pupils vary in size as mediated by cholinergic parasympathetic neurons (which constrict) and adrenergic sympathetic neurons (which dilate). Important factors in pupil size are the level of illumination and physiological arousal, and it also varies unaccountably (hippus). Bilaterally large pupils may represent stimulant, hallucinogen, or anticholinergic intoxication. Unusually small pupils are due to opiate intoxication. Asymmetric pupils usually result from iris trauma or surgery.^{1,2}

Pupillary responses to light (“response”) and near vision (“accommodation”) can be important. The swinging flashlight

test is actually a test of afferent light reception. As the light goes from the healthy eye to the impaired eye (or impaired afferent system), both pupils dilate; both constrict again when the light passes back to the intact side. This finding, known as the Marcus Gunn pupil, is due to optic nerve disease (optic neuritis in particular) or severe retinal disease. Pupillary constriction normally accompanies convergence on a near target. Light-near dissociation, an uncommon finding of pupils constricting briskly with near vision but not on exposure to light, might be due to an afferent CNII lesion (Argyll-Robertson pupil), disrupted parasympathetic efferents (Adie’s tonic pupil), or injury to the dorsal midbrain (dorsal midbrain syndrome or Parinaud’s syndrome). Other features of dorsal midbrain syndrome include lid retraction, loss of upgaze, and other extraocular deficits.^{1,2,6}

Earlier studies in schizophrenia included numerous observations on pupil size, including reactions to psychological stimuli. Anisocoria was found in 5 to 11 percent of patients with schizophrenia, more than in healthy persons.^{7,8} More recently, pupillary findings were no more prevalent in schizophrenia than in health.⁹ Pupil studies are now generally conducted using tightly controlled conditions and instrumentation that cannot be matched in usual clinical settings.

Extraocular movements.

Significant extraocular movement problems generally cause diplopia (although diplopia is due to cranial nerve problems in less than half of cases). Heterotropia (strabismus) of early onset is not associated with diplopia, as only one eye functions.^{1,2}

Impaired upgaze, or raising the eyebrows or forehead during upgaze, may be a Parkinsonian sign,¹⁰ but is also attributed to normal aging. If marked and accompanied by ptosis and complaints of diplopia, myasthenia gravis is likely. Impaired down-gaze

suggests progressive supranuclear palsy,¹⁰ but thyroid myopathy and orbital fractures may be responsible. Isolated lateral gaze palsy is usually due to abducens nerve (CNVI) palsy, commonly associated with diabetes mellitus; sometimes myasthenia gravis and thyroid myopathy can be the cause.^{1,2}

Gaze deviation is fairly common. The frontal eye fields project to contralateral burst neurons in the brainstem. Thus, with a destructive lesion (e.g., stroke) of the frontal lobe, the patient “looks at the lesion.” With an irritative lesion (e.g., hemorrhage), the patient “looks away from the lesion.”⁴

Sustained lateral gaze nystagmus is a sensitive (if nonspecific) sign of metabolic or cerebellar insult. Sedative-tranquilizers, alcohol, diphenylhydantoin, and phencyclidine commonly cause nystagmus. If lateral nystagmus is accompanied by weak adduction of the other eye (difficulty looking across the midline), the problem is probably internuclear ophthalmoplegia; if bilateral, it is strongly indicative of multiple sclerosis, and if unilateral many explanations are possible.^{1,2}

Several oddities of extraocular movement have long been noticed in schizophrenia, including sustained deviations of gaze and abnormal ocular pursuit.¹¹ Smooth pursuit abnormalities have been studied for the past century.¹² One occasionally notes jerky saccades during bedside testing,^{13,14} but smooth pursuit eye movements are now usually the domain of specialized labs.

Failures of convergence seem to be common in schizophrenia: six percent in acute schizophrenia¹⁵ and 18 to 24 percent in chronic schizophrenia.^{16–18}

Nystagmus comes in many varieties, the most common being conjugate horizontal jerk nystagmus with sustained lateral gaze. This type of nystagmus, in which both eyes move together (conjugate) with a slower movement away from the target followed by a rapid

movement (jerk) toward the target, is attributed to cerebellar disease. Intoxication with sedative-tranquilizers, alcohol, and phencyclidine also cause this type of nystagmus. It can also be seen in neurologically sound people, particularly with fatigue. At angles greater than 45 to 50 degrees from directly forward nystagmus has no pathological significance. If rebound nystagmus is seen, cerebellar disease is virtually confirmed. Spontaneous nystagmus, noted without stimulus or demand, is most often seen in vestibular disease, but is also common in those with severe visual impairment.

Nystagmus is more common in schizophrenia than in health and mood disorders, with rates of 5 to 20 percent.^{8,19,20} It is more common in alcoholism (not during intoxication) than common psychiatric disorders.²⁰ Phencyclidine intoxication, which often resembles idiopathic psychosis, presents with nystagmus in more than 50 percent of acute cases.²¹

Strabismus was more frequent in one large sample with schizophrenia (13%) than in healthy controls (4.4%); this was particularly true of exotropia (8.2% vs. 0.6%).²² Strabismus in childhood also predicts adult schizophrenia-spectrum disorder.²³

Eyelids. In the awake person at rest, eyelids usually slightly cover the superior iris but leave a small white gap beneath the inferior iris. Widely separated eyelids, giving the impression of over-arousal or protuberant eyes, is called lid retraction. Related to this is lid lag, in which white cornea is visible between lid and iris during down-gaze. Whether unilateral or bilateral, either sign suggests hyperthyroidism. In fact, these appear to have the highest positive likelihood ratios and specificity among all physical signs of hyperthyroidism.²⁴ Other causes include unilateral ptosis, weakness of the orbicularis oculi or CNVII (nothing opposes lid opening),

previous eyelid surgery, irritating contact lenses, and lesions of the dorsal midbrain.

Ptosis suggests neuromuscular disease, such as myasthenia gravis (pupils are normal), and also a lesion of the oculomotor nucleus or nerve (unilateral, pupil dilated, exotropia, diffuse paresis of eye movements) and Horner's syndrome (sympathetic denervation, pupil constricted, lack of facial sweat).^{1,2}

EXAMINATION METHODS

General inspection of the eyes. Proptosis or exophthalmia can reflect thyroid disease. This is present when the eyes protrude from the contour of the face, when viewed from behind and directly over the crown. The lateral width of the palpebral fissure (apparent size of the eye) can be reduced in fetal alcohol syndrome and several other developmental syndromes. At the medial corner of each eye, the epicanthal fold (obscuring the caruncle) is a common anomaly; its most common pathological significance is Down syndrome (trisomy 21).

Discolorations at the outer margin of the iris can be important. Most common among these is arcus senilis, a brownish-yellow ring. The Kaiser-Fleischer ring, more brownish-green than arcus senilis, strongly suggests Wilson disease.

Pupils. Because of factors such as ambient light, arousal, and attention, subtle variations in pupil size are difficult to interpret in clinical practice. Unusually large and small pupils and anisocoria might be noted with simple observation. Testing the light response should be done in a dimly lit room. The patient is asked to focus on some distant object, even if the view of the object is obstructed. A bright light is passed over the patient's eyes, shining it into each eye for about one second before shifting to the other eye. The normal response is for both eyes to constrict promptly and equally and to dilate slightly during the shift from one eye to the other. In normal

light, during extraocular motor testing, observe the pupils' response during convergence. The normal response is bilateral constriction. It should be noted that in specialized labs pupilometry can reveal the extent of a subject's interest or effort, and can reveal much about autonomic nervous function.²⁵⁻²⁸

Extraocular motor function.

Directly elicited extraocular movements are readily measured and have numerous implications for diagnoses.^{29,30}

Misalignment of the eyes (known as strabismus or heterotropia) is often obvious. In patients who make eye contact, one readily notices those making contact with only one eye. Milder heterotropia is revealed by the corneal light reflex test: Shine a light onto the eyes from a distance and observe the reflection on the cornea with respect to the pupil. The reflection from both eyes should appear symmetric and generally slightly nasal to the center of the pupil. The specific deviation of the poorly functioning eye should be described: exotropia if external (temporal), esotropia if internal (nasal), and hypertropia if superior.

Smooth pursuit movements, the most commonly tested extraocular movements, are tested by asking the patient to visually track a target ("follow this with your eyes only"), and then the clinician moves the target (e.g., the tip of your finger or pen) smoothly to the vertical and horizontal extremes of the patient's tracking ability. The target is held about 12 to 18 inches from the eyes. Also, the target is brought slowly toward the eyes until it is about three inches away or until one or both eyes break convergence and drift outward. During these maneuvers, observe for limitations of movement, loss of fixation, head movements, jerky (rather than smooth) movement of the eyes as they track the target, and nystagmus.

Nystagmus (in this case, gaze-evoked nystagmus) consists of more or less rhythmic excursions from and back to the target. Note

whether or not it is jerk nystagmus (movements from target are slower than movements to target), whether it is conjugate (synchronized bilaterally), and in which gaze direction it occurs. If conjugate lateral jerk nystagmus is prominent, have the patient hold the position for 20 to 30 seconds, by which time jerks should have ceased. When the eyes revert to their resting forward position, observe for rebound nystagmus (a few beats of conjugate jerk nystagmus in a direction opposite to the previous lateral gaze).

When the patient has been asked to track an object with eyes only, head movement (synkinesis) can reflect disinhibition. In this case, try it again after asking the patient more explicitly to hold his or her head still. Asking the patient to maintain fixation on an off-center target is a test for motor imperistence.

Saccades, being more sensitive to supranuclear dysfunction, are probably more useful in psychiatric assessment. Ask the patient to look at one target, then another, then to look quickly back and forth between the two targets. Targets are typically 18 to 24 inches from the eyes. Two sets of targets, separated horizontally and vertically, can be tested.

If saccades or smooth pursuit are impaired, the head impulse test can be useful for localizing further. The patient relaxes the neck as the examiner holds the head on either side. The examiner quickly displaces the head a short distance and observes the eyes. Normally the eyes will displace in such a way as to maintain the direction of gaze (in spite of the changed position of the head). Having been unable to move the eyes in a given direction during saccade or pursuit testing, eye movement in that direction during head impulse testing shows that the problem is supranuclear. An example is supranuclear palsy (a Parkinsonian syndrome), in which downward gaze is impaired except with the head impulse test.^{1,2}

Eyelids. Simple observation of the eyes identifies lid retraction, in which white is visible above the iris. The eyes have a startled, bulging appearance, but without true proptosis. To detect lid lag, observe the upper eyelid as the patient tracks downward during extraocular motor testing. Lid lag is present when the white becomes visible above the iris (or increases in visible extent) during downgaze.

Ptosis is generally unmistakable, with half or more of the pupil obscured in the alert patient.^{1,2}

CONCLUSION

Attention to the functional integrity of cranial nerves III, IV, and VI can yield important information to the psychiatrist. Unusual oculomotor activity is often encountered in psychiatric patients. Pupil size, extraocular movements, nystagmus, lid retraction, lid lag, and ptosis are significant factors to consider when evaluating psychiatric patients. Beyond screening for diseases and localizing lesions, certain tests yield useful information about the individual's higher cortical function, extrapyramidal motor functioning, and toxic/pharmacologic state. There are evaluation techniques that include casual observation and simple tests that require no equipment and can be done in the psychiatrist's office.

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