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Hereditary Nystagmus in Early Childhood

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Nystagmus is defined as a rhythmic involuntary movement of the eyes, and as an acquired phenomenon arising in later childhood or in adult life is usually a symptom of serious neurological or labyrinthine disease; in such cases the movements of the eyes commonly produce subjective symptoms of objects moving in the visual panorama (oscillopsia). Nystagmus may also be 'congenital', or, more accurately, may first be observed within a few weeks of birth when the infant begins to attempt to fix and to follow visually stimulating targets by means of conjugate movements of the eyes. In such cases, the nystagmus may persist throughout life, but even at a later stage there is always a complete absence of the symptom of oscillopsia. Nystagmus which presents in early infancy is often hereditarily determined, and its aetiology is variable, for it may be a symptom of a serious disorder affecting the eyes or the visual pathways, or the central nervous system. In particular, such clinically obvious affections as total albinism, aniridia, and dense cataracts induce nystagmus at a very early age. In the majority of cases, however, no gross abnormality of the eyes is observed on routine clinical examination of the affected infant, and no other abnormality of the central nervous system can be discerned. In many such cases the nystagmus is then an isolated phenomenon due to some as yet undetermined developmental anomaly in the central nervous mechanism concerned with 'steady fixation' of the eyes; such nystagmus is said to be 'extra-ocular' or 'idiopathic'. There is, however, a residue of cases in which in early childhood the nystagmus is in fact due to an hereditarily determined disorder of the visual apparatus which is not apparent on cursory ophthalmological examination, and which may follow a progressive course. The long-term visual prognosis in such cases is usually much worse than in cases of idiopathic nystagmus, and it is therefore very important from the point of view of genetic counselling that these specific ocular causes of nystagmus should be diagnosed at an early age. After describing the clinical characteristics of various types of hereditary nystagmus and the techniques which are available to differentiate between 'idiopathic' nystagmus and nystagmus as a symptom of an occult disorder of the visual apparatus in early childhood, some description of the modes of inheritance and of the long-term visual prognosis are given in the various categories of infantile nystagmus which can be so defined.

Character of Nystagmus

Though it is not usually possible to arrive at an exact diagnosis of the cause of nystagmus by observation of the eye movements alone, a great deal of useful information can be obtained by such a study. The important points are a determination of the direction of the nystagmus (which is arbitrarily defined as the direction of the fast component), the differentiation between pendular and jerky nystagmus, and the distinction between disturbances of the fixation reflexes and of the gaze mechanisms. Pendular nystagmus has equal speed in both directions; jerky nystagmus has a fast and a slow component. Fixation nystagmus is present in forward gaze as well as in other directions of gaze, whereas gaze nystagmus is present only in certain lateral or vertical fields of gaze, and is always an acquired phenomenon. In later childhood and in adult life exact objective records of the characteristics of the nystagmus in any case can be made using the technique of nystagmography, the phenomenon of changing electrical potentials between skin electrodes situated above, medially, inferiorly, and laterally to the eyes, with movements of the eyes being employed to give a permanent record of the ocular oscillations. In infants or young children below the age of 4 years this technique is unsuitable, and reliance has to be placed on skilled clinical observation, possibly supplemented by cinematography; the film of the eye movements then being projected in slow motion to allow further study.

Observations of the involuntary eye movements by these techniques will first allow a differentiation between fixation and gaze nystagmus, and in early childhood fixation nystagmus is by far the commoner

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variety. Secondly, inspection will differentiate between a primarily pendular and a jerky nystagmus, this last observation being of great diagnostic importance.

Types of Hereditary Nystagmus

(a) **Congenital jerky nystagmus.** This variety of nystagmus constitutes the classical form of hereditary nystagmus, and is often termed 'idiopathic familial nystagmus'; the ocular oscillations are noted within the first few days of birth. The nystagmus is most commonly horizontal and is present in all directions of gaze, but with a point of reversal of the fast component which is usually asymmetric, in which the nystagmus is minimal so that the child tends to adopt an abnormal compensatory head posture because of the improved vision which is obtained in that position. The nystagmus is usually reduced in amplitude when the eyes are converged so that near vision is much more acute than distance vision. Because of this, affected children are often capable of education in a class for the normally sighted (despite a corrected distance visual acuity of 6/36 or less), provided that they are allowed to learn mainly from books rather than from the blackboard. The amplitude of the nystagmus tends if anything to become reduced as age increases, so that the long-term visual prognosis is fairly favourable. This type of nystagmus, as is the case in all varieties of jerky nystagmus, is not the result of a disorder of the eyes, which are entirely healthy, but rather of a defect in the ocular posture as the result of abnormal development of the complex centres of the brain-stem which are concerned with the 'steady fixation' of the eyes. The defective vision is due to the blurring of the retinal images, which occurs as a result of the constant oscillatory movements of the eyes.

(b) **Pendular nystagmus.** In contrast to the former condition which is a fairly well-delineated clinical entity, pendular nystagmus occurs in early childhood as a symptom of many hereditary disorders of the eyes and of the visual pathways, and also in some cases in the absence of any demonstrable ocular pathology. Whether there is obvious clinical evidence of ocular disease or not, the character of the nystagmus tends to be the same; pendular horizontal oscillations are present on forwards, upwards, and downwards gaze, but in positions of lateral gaze the nystagmus tends to become jerky, the fast phase then being in the direction of gaze. The hereditary disorders which most commonly produce pendular nystagmus in early childhood in the absence of overt signs of ocular disease, and which it is so important to diagnose at an early age, are Leber's congenital amaurosis (retinal aplasia), congenital cone dysfunction (achromatopsia with amblyopia), the form of optic atrophy which is inherited as an autosomal recessive characteristic, ocular albinism, and macular hypoplasia. The differentiation of these conditions in infancy is facilitated by combining a thorough examination of the ocular media and fundi with the pupils fully dilated under general anaesthesia with various electrophysiological investigations which are modifications of the standard techniques of electroretinography.

Electroretinography. When the healthy retina is stimulated by a bright flash of light, a complex series of changes is induced in the electrical potential of the retinal elements. The sum of these changes can be detected by placing an active electrode on the cornea by means of a contact lens, and earth and reference electrodes on the skin of the face. When amplified and recorded these changes are summated as the electroretinogram (ERG) which has two principal features; an initial a-wave of negative potential and a subsequent b-wave of positive potential. The total amplitude of the normal response in the dark adapted eye is about 250 microvolts, and the changes in potential occur within 200 millisec. of the light stimulus. Experiments have shown that the a-wave is due principally to change occurring in the electrical potential of the outer segments of the retinal receptors, and the b-wave to changes in the retinal bipolar cells, the clinical ERG representing the summation of the changes occurring in the entire retina. In early childhood the investigation must be carried out under general anaesthesia in order to maintain a steady contact between the cornea and the active electrode in the contact lens and also to overcome the child's natural apprehension. The standard ERG in the dark adapted state is a measurement principally of rod function, as it is an index of the mass electrical response of the retina, and the rods far outnumber the cones in that tissue. The function of the cones alone may, however, be assessed by measuring the rate of ERG fusion using a flickering light stimulus. The fusion rate of the cones is high (greater than 30 cycles per second), but that of the rods is low (less than 10 cycles per second). A low ERG fusion frequency therefore indicates a defect in function of the retinal cones.

Leber's Congenital Amaurosis (Retinal Aplasia)

In this condition there is a gross defect in the function of the retinal elements from birth or early infancy, though the eyes may appear completely normal in early childhood. In later life the typical signs of a tapeto-retinal degeneration gradually appear with attenuation of the retinal arteries, hypopigmentation of the choroid, and pathological pigmentation of the retina (so-called 'atypical' retinitis pigmentosa). The long-term visual prognosis is

very poor, but in early life the condition may be impossible to distinguish from an idiopathic nystagmus on clinical grounds alone. The essential diagnostic method at that stage is electroretinography, for the ERG response is grossly attenuated or extinguished even at this early age.

Congenital Cone Dysfunction Syndrome

In this disorder the rods function normally but the retinal cones are defective from birth. As a consequence there is a condition of 'day blindness', with grossly defective colour discrimination and poor central visual acuity. In later childhood subjective testing will show the defect in colour vision, but as the eyes appear entirely normal on ophthalmoscopic examination it is not possible to diagnose the condition in infancy without resort to electroretinography, when the defect in cone function is demonstrated by an abnormally low ERG fusion frequency using a flickering light source.

Hereditary Optic Atrophy

The form of optic atrophy which follows a pattern of autosomal recessive inheritance produces a conspicuous defect in visual acuity from early infancy and consequently induces a pendular nystagmus. It may be difficult to diagnose at that age because the optic discs of normal infants show a very wide variety of appearances, and conspicuous pallor of the discs may be physiological at that age. When optic atrophy is symmetrical and bilateral it may therefore be very difficult to be certain that the pallor of the discs is pathological, so that the nystagmus which is induced by poor central visual acuity in such cases may be considered as 'idiopathic' in the early years of life. The ERG response is of normal amplitude in this condition, as the retinal receptors and bipolar cells are not involved in the degenerative process.

Ocular Albinism

In this condition, body pigmentation is normal and it is the eyes alone that show albinotic changes. As the normal fundus is only lightly pigmented in early childhood, the cause of the nystagmus which is exhibited by such children from early infancy may be overlooked unless particular attention is paid to the degree of pigmentation of the iris root which is obviously defective in this condition. The ERG response is normal.

Macular Hypoplasia and Macular Dystrophy

Pendular nystagmus can be the result of a faulty development or an early degeneration of the maculae, but this may cause little or no disturbance in the ophthalmoscopic appearance of the posterior poles of the eyes in early childhood. However, careful inspection under general anaesthesia with the pupils fully dilated, especially using a binocular microscope, may show an absence of the normal foveal light reflexes and a pathologically featureless appearance of the macular area. As the macular receptors represent only a very small proportion of the total rods and cones in the retina, the ERG response, which is a mass response from all these elements, does not show any significant decrease in potential in these cases and is of no assistance in diagnosis.

'Idiopathic' Pendular Nystagmus

At the present time there is a large residue of cases exhibiting an hereditarily determined pendular nystagmus which arises in the first few months of life and persists throughout life, but is non-progressive, thus giving a relatively good long-term visual prognosis. No specific ocular cause for the nystagmus is discernible in such cases even with the sophisticated methods of clinical examination and electrophysiological investigation described. The fact that the character of the nystagmus is identical to that found in the presence of congenital bilateral ocular defects suggests, however, that many such cases are in fact the result of some specific disorder affecting the visual apparatus, which is not capable of being detected by the present methods of investigation.

Modes of Inheritance (Table I)

With the exception of ocular albinism which is inherited as an X-linked recessive characteristic, the specific disorders of the visual apparatus which may produce nystagmus in early childhood in the absence of overt ocular pathology all commonly exhibit an autosomal recessive mode of inheritance.

'Idiopathic' congenital nystagmus, whether jerky with abnormal head posture, or pendular, most commonly has an X-linked dominant hereditary pattern,

TABLE I

COMMON HEREDITARY PATTERNS OF FIXATION NYSTAGMUS IN EARLY CHILDHOOD

Autosomal Recessive
Optic atrophy
Leber's congenital amaurosis
Congenital cone dysfunction syndrome
Macular hypoplasia
X-linked Recessive
Ocular albinism
X-linked Irregular Dominant
Idiopathic jerky or pendular nystagmus

with suppression of the manifestation in some one-third or one-half of the women carrying the gene. In a few patients there is an X-linked recessive pattern in the inheritance, and in a small number an autosomal recessive mode of inheritance is claimed, though it is most likely that the nystagmus in such cases does in fact have a specific ocular cause which has not been determined because of inadequate investigation.

Visual Prognosis (Table II)

A truly 'idiopathic' or 'extra-ocular' hereditary nystagmus, whether jerky or pendular in character, may persist throughout life. Being unassociated with any ocular disorder, however, it carries a moderately good long-term visual prognosis. In contrast, the specific occult ocular disorders which have been described carry a much worse long-term visual prognosis. The importance in genetic counselling of the early exact differentiation of these disorders, particularly in sporadic cases, is thus readily understood.

TABLE II

VISUAL PROGNOSIS OF HEREDITARY NYSTAGMUS IN EARLY CHILDHOOD

Aetiology	Natural History	Visual Prognosis
Idiopathic jerky or pendular nystagmus	Non-progressive	Moderate to good
Ocular albinism	Non-progressive	Moderate
Macular hypoplasia	Non-progressive	Moderate
Congenital cone dysfunction syndrome	Non-progressive	Moderate to poor
Optic atrophy (type exhibiting autosomal recessive inheritance)	Progressive	Poor
Leber's congenital amaurosis (retinal aplasia)	Progressive	Very poor

In summary, the paediatric ophthalmologist or clinical geneticist faced with a young child with nystagmus in the absence of obvious ocular pathology must do his utmost to arrive at an early definitive diagnosis. Where other members of a family are already similarly affected, the mode of inheritance and the natural history of the disorder which has previously been exhibited make the task of genetic counselling, and of assessment of long-term visual prognosis, fairly straightforward, with an emphasis on the fact that an autosomal recessive mode of inheritance usually infers the presence of a severe and possibly progressive ocular disorder. In a sporadic case, however, it is of the greatest importance that detailed examination and electrophysiological investigation along the lines described should be undertaken before firm advice of any sort is offered to the child's parents.

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