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C04

Clinical Electrophysiology in Paediatrics

6 June 2015

14:30-16:00hrs

Hall L1

HAND-OUTS

Maturation of the ERG and VEP

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As with all physiological measurements, it is essential to know what a normal VEP or ERG looks like. Acquisition of normative data is required by the Standards of the International Society for Clinical Electrophysiology of Vision in order to provide decision limits for a test outcome parameter. The rapid maturation of the visual system in the earliest years of life makes collection of electrophysiological normative data a substantial undertaking.

ERG maturation comprises shortening peak times and increasing amplitudes of its constituent waves, reflecting retinal neural and vascular tissue development. Retinal maturation remains incomplete at birth: photoreceptor outer segments are scarcely half their adult length, and the fovea remains poorly formed, still containing inner nuclear layer neurons. Rod-system sensitivity at birth as measured by the ERG is around 0.6 log units poorer than adult sensitivity, and ERG maximal amplitudes are only around 10% of adult values. Sensitivity matches adult values by 6 months while amplitudes reach adult values by 12 months. Cone-system ERGs show faster maturation than rods. The pattern ERG peak times are adult-like by around 6 months, and amplitudes peak at around 6 years of age. The multifocal ERG in 10-week infants has amplitudes around half those of adults, with slower peak times; over 10 years of age, there is a reduction of amplitude and increase of peak times of first- and second-order components: few data are available for intermediate ages. Premature birth, even in the absence of retinopathy of prematurity, confers functional deficits which persist into childhood.

VEP maturation reflects maturation of the fovea and the visual pathways. The fovea remains immature at four years, while myelination in the optic nerve and tracts is not mature until around 5 years. In the lateral geniculate nucleus and cortex, dendrites and spines increase in number during the first postnatal months before decreasing to adult-like levels by the second year. Similarly, cortical synaptogenesis is rapid after birth, being maximal at about 8 months before being pruned to reach adult-like numbers at about 11 years. Parvocellular pathways mature more rapidly than magnocellular pathways. The flash VEP at birth is a simple, slow deflection, which rapidly develops complex morphology during the first six months. Early components become adult-like by one year, but later components remain immature until after five years of age. Transient pattern reversal VEPs, originating in the primary visual cortex, are evident from birth providing the pattern size can be resolved. For 60’ checks (0.71 cpd for the fundamental spatial frequency), peak time of P100 reduces sharply from >200ms in the first weeks of life to an adult-like 100ms by 12 months of age. Amplitude generally increases but is highly variable. Maturation is slower for smaller patterns. Steady-state VEPs can be used to measure spatial frequency VEP threshold, which improves from around 5 cpd in the first month to 10 cpd or better by 6 months of age. The multifocal VEP has been investigated a little in normal paediatric populations, and shows increasing amplitudes and reducing peak times up to 13 years of age.

Paediatric Electroretinography (ERGs)

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Electrophysiological testing provides an objective and non-invasive method for visual pathway evaluation. Electrophysiology therefore has a privileged position in the child with retinal disease, who may not accurately be able to describe their symptoms. It enables the distinction between disorders that may present with similar signs and/or symptoms and facilitates the differentiation between benign or severe, progressive or stationary disorders. Complementary use of different electrophysiological procedures allows accurate characterisation and localisation of dysfunction. For example, EOG reflects the function of the photoreceptor/RPE interface; the ERG, rod and cone photoreceptor and inner retinal function; the PERG, macular and central retinal ganglion cell function; and the VEP intracranial visual pathway function. It should always be remembered that VEP delays and abnormalities are non-specific; delays are commonplace in eyes with macular dysfunction. Such eyes may have normal structural imaging; normal structure does not mean normal function! Electrophysiological phenotyping has become increasingly important as genotyping have increased and new therapies developed; accurate phenotyping can facilitate focused molecular screening in patients with atypical features.

The techniques for recording ERGs in young children and infants will be described, along with those used in older children and adults, and clinical

examples shown to illustrate the diagnostic value of ERG in various disorders, both inherited and acquired. For example, the findings in retinitis pigmentosa (rod-cone dystrophy), commonly associated with nyctalopia, will be compared and contrasted with those of congenital stationary night blindness. The former, being caused by photoreceptor dysfunction, shows reduced dim flash ERGs (rod-specific, DA 0.01) accompanied by marked a-wave reduction in the bright flash dark-adapted ERG (DA 10.0); the latter also shows reduced dim flash ERGs (rod-specific, DA 0.01), but the bright flash dark-adapted ERG (DA 10.0) contains a normal a-wave but a reduced b-wave (a "negative" or "electronegative" ERG waveform), confirming normal photoreceptor function and establishing inner retinal dysfunction. A further disorder associated with night blindness, fundus albipunctatus (*RDH5* mutation), will be used to illustrate not only the power of electroretinography to reveal the pathophysiological mechanisms underlying the disease, but also the need always to consider such mechanisms when determining whether the ISCEV Standard ERGs, a minimum data set, can actually answer the clinical question. Another disorder often associated with night blindness is vitamin a deficiency which illustrates the ability of the ERG not only to make a diagnosis but also objectively to assess the response to therapeutic intervention. The concept of "diagnostic" or pathognomonic ERGs will also be discussed.

Electrophysiological investigation in the child with nystagmus

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In the child nystagmus can develop already in the first months of life because of retinal or vitreoretinal, foveal or visual pathway dysplasia, abnormality.
Diagnostic approach is clinical diagnosis with neuroimaging, and genetics, while electrophysiological examination is of great diagnostic importance, especially in non-verbal children, in visual deficit with clinically normal fundi and in looking for asymmetries, in addition it is objective and non-invasive.
The electrophysiological recordings of infants with nystagmus and retinal or post-retinal visual pathway dysfunction should be compared with normative data, age-matched healthy children.
Electrophysiology in paediatric ophthalmology can provide global, objective viusal function evaluation, it is adjusted to child's age, cooperation, with no direct correlation with any optotypes. So far there are no method standards for infants and toddlers, the approach is separate or simultaneous electroretinography (ERG), visual evoked potential (VEP) recording. Electrophysiological recording methods in infants, small, and school children are demonstrated.
In infants and small children simultaneous ERG/VEP recording, peformed in alert child, with no pupil dilation, skin electrodes fixed on the lower eye lid for flash ERG, and 3 electrodes over the visual cortex for VEP, provides information on the level of visual system lesion (protocol Great Ormond Street Hospital for Sick Children, London).
In school children International Society for Clinical Electrophysiology of Vision (ISCEV) standards can be implemented in recording scotopic – photopic ERG, multi focalERG, pattern ERG, VEP to full and half field stimulation.
Flash ERG and VEP recordings are shown in infants with nystagmus due to retinal disorders e.g. Leber's congenital amaurosis (LCA), achromatopsia, early onset retinal dystrophy (EORD). In LCA, a very heterogenous retinal dystrophy with rods and cones maldevelopment, there is ususally extinguished ERG and VEP, however in some patients with some preserved vision, there will be no ERG, but attenuated VEP activity. In achromatopsia, cone mediated activity, tested with red flash, and with 30 Hz flicker is not detectable, while rod mediated activity , evoked by dim blue flash, delivered under scotopic conditions, is well preserved.
ERG techniques can differentiate between complete and incomplete congenital stationary night blindness (c, i CSNB). In both types of CSNB there is an electronegative waveform of the combined rod-cone responses in standard full-field ERG. In cCSNB complete rod dysfunction was evident and borderline cone dysfunction, while in iCSNB there was some preservation of rod function and severe cone dysfunction. ON-OFF ERG reveals ON-bipolar cell dysfunction with cCSNB, and ON and OFF bipolar cell dysfunction in iCSNB.
A normal ERG and non-recordable VEP indicate the visual pathway lesion e.g. severe optic nerve hypoplasia, neurological problems with compressive lesions (tumours, osteopetrosis), metabolic problems (Tay Sachs).

VEP ipsilateral or uncrossed asymmetry defines the absent nerve fibre decussation at the chiasm – in the association with achiasmia or chiasmal hypoplasia.
VEP contralateral or crossed asymmetry as found in albinism shows that from the left eye all of the optic fibres project to the left occipital cortex, where a negative wave from around 80 ms is elicited, wheras over the right occipital cortex there is a positive wave of around 80 ms – the other end of the dipole activation, and from the right eye the flash distribution is reversed.
Electrophysiology is esential and sensitive in identifying no obvious sensory defect, clinical – electrophysiological correlation is evident. Follow-up is necessary in determinig the defect severity, progression. The underlying disorder in congenital nystagmus can be identified clinicaly and electrophysiologicaly in up to 80 % already in the first months of life.

References

Apkarian P, Reits D, Spekreijse H, Van Dorp D. A decisive electrophysiological test for human albinism. Electroencephalogr Clin Neurophysiol 1983; 55: 513- 31.

Apkarian P, Bour L, Barth PG. A unique achiasmatic anomaly detected in non-albinos with misrouted retinal-fugal projections. Eur J Neuroscience 1993; 6: 501-7.

Brecelj J, Stirn Kranjc B. Visual electrophysiological screening in diagnosing infants with congenital nystagmus. Clin Neurophysiol 2004; 114: 53-65.

Fulton AB, Brecelj J, Lorenz B, Moskowitz A, Thompson DA, Wesall C. ISCEV Committee for pediatric clinical electrophysiology guidelines. Pediatric clinical electrophysiology: a survey of actual practice. Doc Ophthalmol 2006; 113: 193-204.

Holder GA, Robson A. Paediatric electrophysiology: A practical approach. In: Lorenz B, Moore AT. eds. Pediatric ophthalmology, neuroophthalmology, genetics. Essentials in ophthalmology Vol 7. Berlin: Springer; 2006: 133-55.

Kriss A, Jeffrey B, Taylor D. The electroretinogram in infants and young children. J Clin Neurophysiol 1992; 9: 373-93.

Kurent A, Stirn Kranjc B, Brecelj J. Electroretingraphic characteristics in children with infantile nystagmus syndrome and early onset retinal dystrophies. Eur J Ophthalmol 2015; 25: 33-42.

Thompson DA, Kriss A, Chong K, et al. Visual evoked potential evidence of chiasmal hypoplasia. Ophthalmology 1999; 106: 2354-61.

Thompson DA, Liasis A. Pediatric visual electrodiagnosis. In: Taylor D, HoytC, eds. Pediatric Ophthalmology and Strabismus. 3rd ed. Amsterdam: Elsevier Saunders; 2005: 87-96.

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Clinical Electrophysiology in Paediatric Practice

Visual Electrodiagnostic Surveillance. 'Should I do it again?'

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introduction

Visual Electrophysiology has an essential role in paediatric ophthalmology practice. The combination of ERGs and VEPs offers an objective and non-invasive assessment of the function of the eye and visual pathways. The results obtained from alert infants and children can localise the site of dysfunction and provide a diagnosis, sometimes even implicating a gene or specific protein, e.g. a pathognomic ERG or VEP features of chiasmal misrouting of albinism. Otherwise the results can direct the need for further investigations, for example metabolic or neurological examinations or MRI imaging, and inform your management plan.

background

At Great Ormond Street Children's Hospital in London we carry out visual electrophysiological assessments on patients who, in addition to ocular problems, often have complex systemic and neurological problems. Most children are ≤2yrs, upper limit 16-18years, and ERGs and VEPs are carried out without sedation or anaesthesia. Many patients are seen just once for diagnostic purposes, but a substantial proportion will attend specialist clinics for visual electrophysiological surveillance.

evidence for repeatability- examples

ERG: Hamilton R et al Docum Ophthalmol 2015 130:83-101
PVEP: Mellow T et al Docum Ophthalmol 2011 122:133-139
PVEP: Sarnthein J et al 2009 Clin Neurophysiol 2009 120:1835-40

reasons for surveillance

Structure does not predict function, [e.g. the fundus can look normal in patients with severe early onset retinal dystrophy, an optic nerve with a glioma may support good visual acuity]. Particularly during times of rapid growth and maturation, when there is plasticity, it is valuable and appropriate to repeat visual electrophysiological tests in the same patient. The results may be used to

i. to distinguish progressive from stationary disease
ii. to plan the timing of intervention of treatment
iii. to understand the natural history of a disease and it's pathophysiology

Case studies will highlight some clinical questions that surveillance may answer

1) visual maturation
   - when to operate on partial congenital cataracts ?
     i. too early increase risk of glaucoma

ii. too late increase risk of bilateral amblyopia

applicable to all infants at risk of amblyopia e.g. due to ptosis, haemangioma, corneal opacity etc.

2) working with normal reference ranges for age
   - is an ERG at the 5th centile suspicious if sensorineural deafness too ?
   - is cone dysfunction stationary or will rods become involved too?
3) assess effect of new treatments on vision outcome
   - can fix and follow adequately monitor infant vision in Rb treatment?
4) assess the visual pathway function
   - do we need to use ICP bolts to assess raised ICP in craniosynostosis

Pattern VEP surveillance of children with craniofacial anomalies in whom complex multifactorial interactions contribute to raised intracranial pressure reduced the number of surgical ICP bolt procedures.

   - is there encroaching visual impairment e.g. chiasmal glioma

5) discrepancies between visual electrophysiology and behavioural vision
   - VA better: optic atrophy
   - VA worse: cerebral visual impairment

VEP vision level & recognition acuity are different measures from different generators. VEPs assess functional integrity of the visual pathway to level 4 of the striate cortex recognition VA requires association areas. The association between VEP vision levels and VA will depend upon the clinical condition.

… And of course a minority of young patients will present with suspicious test findings under less than ideal recording conditions. Communication of co-operation is key for clinical weighting of results. It is completely acceptable to seek subsequent confirmatory findings to account for the confounding effects of poor co-operation.

Some recommendations to get the most from paediatric ERGs and VEPs,

- Attend the recording: artefacts from lively children can mimic responses.
- Combine both ERG and VEP for each patient.
- Use a trans-occipital array of VEP electrodes.
- Use different stimulus sizes and presentation modes on the same patient.
- Longitudinal ERG and pVEP follow up should not depend only on the comparison of one measurement, e.g. peak latency, over time. Rather, a holistic comparison of waveforms is needed which will offset any expected maturational change, over a number of stimuli.

Results are a snap shot in time - always review results in clinical context.

Early onset retinal dystrophies: diagnosis and potential for treatment

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Introduction

To date, mutations in 28 different genes have been associated with early onset retinal dystrophies EOSRDs as the molecular genetic basis of up to 80% of EOSRDs. Gene replacement therapy is currently tested in one form i.e. RPE65 deficiency, and oral administration of 9-cis-retinyl acetate in 2 forms, i.e. RPE65 deficiency and LRAT mutations. In the course, specific diagnostic aspects of the different forms of EOSRD will be discussed as well as read-out paraemters for natual history studies and clinical trials ,the latter for RPE65 deficiency and LRAT mutations.

Results

The genes involved in EOSRDs are listed in table 1.
For the majority of genes, Ganzfeld ERG and mf ERG are non-recordable at the time of diagnosis although visual acuity and visual fields may be testable for many years. At best, microvoltage flicker ERG may be measurable in some forms. The hope that after gene replacement and substrate replacement therapy, ERGs may become measurable as in the corresponding animal models has not been fulfilled. Read-out parameters for both, natural history and treatment trials often are psychophysical i.e. subjective tests such as visual acuity and visual fields. In addition, imaging, mainly SD OCT and possibly also adaptive optics AO of individual photoreceptor inner and outer segments, are promising tools to quantify residual functional potentials.

Discussion

Recently, long term results of gene therapy trials for RPE65 deficiency have been published [3,5,7]., as well as short time results on oral administration of 9-cis-retinyl acetate in 2 forms, i.e. RPE65 deficiency and LRAT mutations [9]. Gene replacement therapy shows an increase in dark adapted retinal sensitivities indicating some improvement in rod response, and formation of a new preferred retinal fixation point (pseudofovea) in some. ERGs did not improve, and, as a disappointment, retinal degeneration continued in the treated areas. These results were different from the animal trials where sustained rescue of retinal function including measurable ERGs was observed. The data with oral administration of 9-cis-retinyl acetate in 2 forms, i.e. RPE65 deficiency and LRAT mutations, rely mostly on psychophysical results and are debatable.
Reasons for the limited clinical results will be analyzed and discussed.
Research today focusses on definitions of new and more sensitive read-out parameters, and in the field of gene therapy on improved vectors and alternative methods such as gene editing. New read-out parameters such as fullfield stimulus threshold FST, quantitative retinal layer analysis on SD-OCT, and fundus-controlled perimetry will be discussed. The clinical value of actual therapeutic approaches remains limited.

Literature

1 Ajmal M, Khan MI, Neveling K, Khan YM, Azam M, Waheed NK et al. A missense mutation in the splicing factor gene DHX38 is associated with early-onset retinitis pigmentosa with macular coloboma. J Med Genet 2014; 51(7):444-448
2 Aldahmesh MA, Al-Owain M, Alqahtani F, Hazzaa S, Alkuraya FS. A null mutation in CABP4 causes Leber's congenital amaurosis-like phenotype. Mol Vis 2010; 16:207-212
3 Bainbridge JW, Mehat MS, Sundaram V, Robbie SJ, Barker SE, Ripamonti C et al. Long-Term Effect of Gene Therapy on Leber's Congenital Amaurosis. N Engl J Med 2015;

4 Chacon-Camacho OF, Zenteno JC. Review and update on the molecular basis of Leber congenital amaurosis. World J Clin Cases 2015; 3(2):112-124
5 Cideciyan AV, Aguirre GK, Jacobson SG, Butt OH, Schwartz SB, Swider M et al. Pseudo-fovea formation after gene therapy for RPE65-LCA. Invest Ophthalmol Vis Sci 2014; 56(1):526-537
6 Estrada-Cuzcano A, Koenekoop RK, Coppieters F, Kohl S, Lopez I, Collin RW et al. IQCB1 mutations in patients with leber congenital amaurosis. Invest Ophthalmol Vis Sci 2011; 52(2):834-839
7 Jacobson SG, Cideciyan AV, Roman AJ, Sumaroka A, Schwartz SB, Heon E et al. Improvement and Decline in Vision with Gene Therapy in Childhood Blindness. N Engl J Med 2015;
8 Kmoch S, Majewski J, Ramamurthy V, Cao S, Fahiminiya S, Ren H et al. Mutations in PNPLA6 are linked to photoreceptor degeneration and various forms of childhood blindness. Nat Commun 2015; 6:5614. doi: 10.1038/ncomms6614.:5614
9 Koenekoop RK, Sui R, Sallum J, van den Born LI, Ajlan R, Khan A et al. Oral 9-cis retinoid for childhood blindness due to Leber congenital amaurosis caused by RPE65 or LRAT mutations: an open-label phase 1b trial. Lancet 2014; 384(9953):1513-1520
10 Peluso I, Conte I, Testa F, Dharmalingam G, Pizzo M, Collin RW et al. The ADAMTS18 gene is responsible for autosomal recessive early onset severe retinal dystrophy. Orphanet J Rare Dis 2013; 8(1):16
11 Wang X, Wang H, Cao M, Li Z, Chen X, Patenia C et al. Whole-exome sequencing identifies ALMS1, IQCB1, CNGA3, and MYO7A mutations in patients with Leber congenital amaurosis. Hum Mutat 2011; 32(12):1450-1459

Table 1

Loci annotated by OMIM				
Locus:	**OMIM:**	**Gene:**	**Gene OMIM:**	**Reference**
LCA1	204000	GUCY2D	600179	[3]
LCA2	204000	RPE65	180069	
LCA3	604232	SPATA7	609868	
LCA4	604393	AIPL1	604392	
LCA5	604537	C6ORF152	611408	
LCA6	613826	RPGRIP1	605446	
LCA7§	613829	CRX	120970	
LCA8	613835	CRB1	604210	
LCA9	608553	NMNAT1	608700	
LCA10	204000	CEP290	610142	
LCA11§	204000	IMPDH1	146690	
LCA12	610612	C1ORF36, RD3	610412	
LCA13	612712	RDH12	608830	
LCA14	604863	LRAT	604863	
LCA15	204000	TULP1	602280	
LCA16	614186	KCNJ13	603208	
LCA17	204000	GDF6	601147	
Further published genes				
EORPMC		DHX38, PRP16	605584	[1]
LCA	204000	IQCB1	609237	[4]
		CABP4	608965	[2]
		ALMS1	606844	[7]
		MyoVIIa	600060	[7]
		CNGA3	600053	[7]
		PNPLA6	603197	[5]
EOSRD	608454	ADAMTS18	607512	[6]
Novel genes				
		ASRGL1		ARVO 2015, Abst. 4348
		CLUAP	609212	ARVO 2015, Abst. 4349
		CCT2	605139	ARVO 2015, Abst. 5424

§Autosomal dominant., all other forms are autosomal recessive