Vigabatrin associated retinal dysfunction in children with epilepsy

R Koul, A Chacko, A Ganesh, S Bulusu, K Al Riyami

Abstract

***Background*—Recent reports have established that eye changes occur in patients treated with vigabatrin.**

***Aim*—To identify the eye changes associated with vigabatrin, based on a prospective study of children treated for seizures.**

***Methods*—Twenty nine children on vigabatrin (mainly as add on therapy) were followed up for 6.5 years. Ophthalmic examination was performed before starting treatment and then six monthly in the outpatient clinic.**

***Results*—Twenty one children fulfilled the inclusion criteria. Most had epileptic syndromes with infantile spasms—namely West syndrome, Lennox–Gastaut syndrome, and partial seizures. Vigabatrin dose was 25–114 mg/kg/day (mean 55.8); duration of therapy was 6–85 months (mean 35.7). Four children (19%) developed eye changes (retinal pigmentation, hypopigmented retinal spots, vascular sheathing, and optic atrophy). Visual evoked potentials were abnormal in 16 children. Electroretinography and electro-oculography, which could have picked up eye changes in early stages, were not performed, as this facility was not available.**

***Conclusions*—Vigabatrin causes eye damage. Most children with epileptic syndromes on vigabatrin cannot complain of their eye problems, hence 3–6 monthly ophthalmic follow up is strongly advised, along with regular electroretinography, electro-oculography, and visual evoked potentials if possible.**

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Vigabatrin (VGB) is used as a first line drug in infantile spasms (IS) and as add on therapy in partial seizures.[1] When the drug was introduced for human use, no serious toxic effects were known. Intramyelic oedema and brain vacuolation were reported in rodents and dogs.[2] VGB is an irreversible inhibitor of γ-aminobutyric acid (GABA) transaminase, thus raising concentrations of GABA in the brain. This effect also occurs in the retina and may even raise GABA concentrations more than those in the brain.[3] Occasional visual field loss with VGB was reported about 15 years ago.[4] Recent reports estimate the incidence of field loss from 50 to 70%.[5 6] In addition to changes in the retina and retinal vessels, optic atrophy has also been reported recently.[7 8] Many studies in adult patients have been published,[5 9 10] but there are very limited published data for children.[6 11 12] The purpose of our prospective study was to identify eye abnormalities in a group of children with epileptic syndromes and partial seizures on VGB therapy.

Methods

Sultan Qaboos University Hospital is a national tertiary care centre where all children with neurological disorders, particularly refractory seizures, are referred for management. VGB has been available in this hospital since 1993. The children with IS, especially West syndrome (WS) and Lennox–Gastaut syndrome (LGS), and other refractory seizures were given VGB as an add on drug. VGB has been used as monotherapy in a few children with IS in the last few years.

All children were developmentally assessed and had detailed systemic and neurological assessment. The seizure types/epileptic syndromes were diagnosed according to the commission on classification and terminology of the international league against epilepsy.[13] Investigations included complete blood counts, renal and liver function tests, serum lactate, ammonia, and creatine kinase. Serum amino acids and blood gases were performed if indicated. Electroencephalography and computed tomography or magnetic resonance imaging of brain were performed in all patients.

Detailed ophthalmic examination was carried out in all cases at the time of admission, including detailed fundus examination under sedation (oral chloral hydrate). The pupils were dilated with 0.5% cyclopentolate and 2.5% phenylephrine, 1 drop every 10 minutes for 20 minutes. Fundus examination was carried out by direct and indirect ophthalmoscopy. The optic nerve, macula, and the retinal periphery were examined in detail. All findings were recorded in the case notes for future comparison and follow up.

Visual evoked potentials (VEP) with light emitting diode (LED) goggles could be performed in only a few children initially; however these were done in 21 cases during the last six months of the study. For this procedure[14] a Nicolet LED goggle stimulator (model 105 A) was used with a Nicolet Viking IV EMG/EP machine. All patients were sedated with chloral hydrate and made to lie supine in a dimly illuminated room at 25°C. Silver/silver chloride electrodes were applied according to the international 10–20 system on Oz, Cz, and Fpz; impedance was always less than 5 Kohms. The LED goggle stimulator was strapped to the patients' eyes after connecting the electrodes to

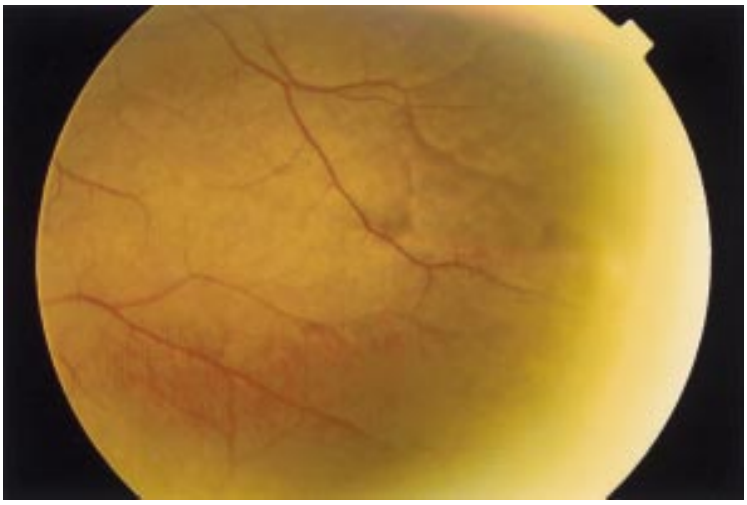

Figure 1 The periphery of the fundus showing mottled appearance with pigment disturbance.

the preamplifier. One hundred responses were averaged by monocular stimulation between a band pass of 0.5 Hz (low frequency filter) and 100 Hz (high frequency filter). The display sensitivity was 10 uv/div and the stimulus rate 1.3 Hz. Two sets of 100 responses were averaged for each eye tested, to ensure that they are reproducible. The superimposed responses were then marked for measuring the amplitude between the positive and negative peaks, and P100 latency of the VEP complex. Normal values for the latency and amplitude were taken from the study.[15]

All children were followed up three monthly in the paediatric neurology clinic and six monthly in the ophthalmology outpatient department. Only children who had both ophthalmic examination and VEP were included in the study. Children who did not attend for follow up, stopped medication in between visits, or did not come for VEP, were excluded from the study. Twenty one children fulfilled the inclusion criteria. Electroretinography (ERG) and electro-oculography (EOG) were not performed, as these procedures were not available to us. Perimetry was not tried in any of the patients, as this was impossible in these children with psychomotor retardation.

Results

Twenty nine children (18 boys, 11 girls) who had taken VGB for more than six months were included. Only 21 fulfilled the required criteria. VGB was used mainly as an add on drug, but three children were receiving it as monotherapy. The age of onset of seizures ranged from birth to 5 years, with a mean of 13 months. There were nine children with epileptic syndromes (six WS, three LGS), five with partial seizures, six with mixed seizures, and one with tonic–clonic seizures. Psychomotor retardation was observed in 17 children (80%). The dose of VGB was 25–114 mg/kg/day (mean 55.8) and duration of therapy was 6–85 months (mean 35.7).

Four children (19%) with VGB as an add on drug, developed eye changes in the form of retinal pigmentation, hypopigmented retinal spots, and optic atrophy. Three of these children had peripheral pigment disturbances (fig 1), hypopigmented retinal spots, and retinal vessel sheathing, the macula and discs being normal. One child developed optic atrophy. The dose of VGB was 25, 50, and 50 mg/kg/day respectively in the group with pigment disturbances and 50 mg/kg/day in the child with optic atrophy. The duration of therapy was 33–81 months.

VEP, performed in 21, revealed normal evoked potentials in five and abnormal evoked potentials in 16 (two of these had ophthalmic and VEP abnormalities at the beginning of therapy as a result of underlying diseases associated with seizures).

Discussion

The effects of VGB on retina are not surprising, as GABA is an established inhibitory neurotransmitter in the vertebrate retina, and occurs in retinal horizontal and interplexiform cells as well as in many types of amacrine cells.[7 16 17] GABA has also been implicated as a regulator of cone synaptogenesis in newborn rabbits.[18] There is a preferential cone system dysfunction in retina with VGB.[7] Occasional visual field defects reported earlier, are thought to be insignificant.[4] Recent reports indicate symptomatic and asymptomatic retinal involvement in 50–70% patients on VGB compared to controls.[5 6 11] Other than visual field defects, ophthalmic findings noted were narrowed retinal arteries, surface wrinkling retinopathy, and abnormal macular reflexes.[6] The usual complaints in such patients are field restrictions or blurred vision. The eye changes occur both during monotherapy and add on therapy.[7] In a recent report, four of 38 patients (10.5%) had retinal involvement, two being on VGB alone.[7] There has been concern whether duration and dose of therapy is related to retinal changes. The duration of therapy seems to be unrelated, as an effect has been seen as early as 2–40 months after starting treatment.[7] Some studies suggest dose related effects and recommend dose reduction in patients whose seizures have been controlled with VGB, when previously the seizures had been refractory.[7] Another study suggests that VGB induced retinal damage is irreversible, except in minimally affected cases, where it may be reversible on withdrawal of the drug.[9] A recent report found complete recovery of visual field constriction following discontinuation of VGB.[19]

Four of our 21 patients on VGB had retinal changes, three of whom had pigment changes and hypopigmented retinal spots, while one had optic atrophy (table 1). In children with tuberous sclerosis, who had baseline retinal hamartomas, it was difficult to assess retinal changes on VGB.

There are a few reports available regarding visual field changes associated with other antiepileptic drugs (AEDs), particularly sodium valproate and carbamazepine.[10 20 21] Combination therapy of sodium valproate and VGB has been reported to produce severe visual impairment in some patients.[21] Sodium valproate and carbamazepine have been in use in millions of

Table 1 Patient details

							Vigabatrin					
No.	*Age of onset, sex*	*Seizure type*	*Development*	*Associated disease*	*EEG*	*CT/MRI*	*Start*	*Dose/kg*	*Duration (months)*	*Other AEDs*	*Ophthal exam*	*VEP*
1	1y 6m, M	LGS	Delayed	TS	S/SW	SGN	Dec93	114	85	SVA	N	N
2	6m, M	PS	Delayed	—	S	N	Apr94	50	81	CBZ	ABN pig	ABN
3	10m, F	Mixed	Vegetative state	Aicardi syndrome	Hyp	CCA	Feb95	50	71	SVA	ABN, OA	ABN
4	**3m, M	IS	Delayed	—	Hyp	N	Apr95	70	69	—	N	—
5	**5.5m, M	IS	Delayed	—	Hyp	N	Aug95	62.5	65	SVA, CLA, ACTH	—	—
6	**8m, F	LGS	Delayed	TS, autistic	MFS	SGN	Sep95	62.5	64	TOP	–	—
7	**4m, F	LGS	Delayed	TS, rt hemiparesis	MFS	SGN	Sept95	62.5	64	LTG, TOP, PHB	—	—
8	1d, F	TC	Delayed	—	SW	N	Jan96	25	60	SVA, ETHO	N	ABN
9	**5y, M	PS, sec gen	N	N	Partial with sec gen	N	Oct96	33	12	PHT	—	—
10	1m, M	TC, MYO	Delayed	Zellweger syndrome	MF	Cortical atrophy	Dec96	36	48	SVA	Previously ABN	Previously ABN
11	3y 6m, M	LGS	Delayed	Down's syndrome	MF, BS	N	May97	25	44	SVA, CLZ	Peripheral pig disturbances, pig spots disc/maula-N	ABN
12	6m, F	PS, SE	Delayed	Microcephaly	SW	N	Jun97	58.8	43	SVA, PHT	N	ABN
13	**10m, M	PS, SE	Delayed	—	Hyp + PS	N	Jul97	50	42	PHT, PHB	N	—
14	**6m, F	IS	Delayed	—	SW, Hyp	N	Jul97	25	42	CLZ, SVA, ACTH	N	—
15	1d, M	TC, MYO	N	Familial seizures	SW	N	Sep97	40	40	PHB+PHT+ CBZ	N	ABN
16	2y, M	LGS	Delayed	—	SW, BS	N	Sep97	62.5	36	PHT+SVA	N	ABN
17	3m, M	IS	Delayed	—	Hyp	N	Mar98	50	33	SVA, CLZ	Pig retinopathy (No change in 1 year)	ABN
18	4.5m, M	IS	Delayed	—	Hyp	Cortical atrophy	Mar98	79.8	33	SVA	N	N
19	3y, F	CPS, TC	N	—	Bitemporal+ generalised	N	Jul98	42	30	CBZ	N	ABN
20	5m, F	IS	N	SCA	Hyp	SGN	Oct98	58	27	—	TS changes	N
21	3m, F	IS	Delayed	Microcephaly, Aicardi syndrome	Hyp	CCA	Dec98	111	25	CLZ	N	ABN
22	1m, M	TC, MYO	Delayed	—	PS	Cortical atrophy	Jan99	50	24	—	Previously ABN	Previously ABN
23	3.5m, F	TC, SE	Delayed	Aicardi syndrome	Hyp	CCA	Mar99	68	22	SVA, PHB	N	ABN
24	5m, M	IS	Delayed	NF1 (father+)	Hyp, BS	Cortical atrophy	Oct99	75	15	SVA	N	ABN
25	**4y 8m, F	PS	Delayed	—	MFS	N	Oct99	50	15	CBZ, SVA	—	—
26	2y 6m, M	PS, TC, SE	N	—	PS with Sec Gen	Hamartom a Angioma	Dec99	35	13	CBZ	N	ABN
27	5m, M	IS	Delayed	—	Hyp	N	Jun00	90	6	—	N	ABN
28	6.5m, M	PS, SE	Delayed	Birth asphyxia	Rt Temporal S	Cortical atrophy	Apr00	40	9	PHB+PHT	N	N
29	6m, M	PS	Delayed	TS	Temporal spikes	SGN	Jul00	62.5	6	—	N	N

ETHO, ethosuximide; SGN, subependymal glial nodule; N, normal; PHT, phenytoin; CCA, corpus callosum agenesis; ABN, abnormal; CBZ, carbamazepine; SVA, sodium valproate; OA, optic atrophy; CLZ, clonazepam; Pig, pigmentary; SCA, sickle cell anaemia; TOP; topiramate; LTG, lamotrigene; PHB, phenobarbital; LGS, Lennox–Gastaut syndrome; PS, partial seizures; Mixed, mixed seizures; IS, infantile spasms; TC, tonic–clonic seizures; Sec Gen, secondary generalisation; SE, status epilepticus; MYO, myoclonic seizures; CPS, complex partial seizures; TS, tuberous sclerosis; NF1, neurofibromatosis type I; SW, spike wave; S, slowing; Hyp, hypsarrhythmia; MFS, multifocal seizures; BS, burst suppression; **excluded from the study.

Table 2 VEP and ophthalmological examination in patients on vigabatrin

					VEP– P100							
			Vigabatrin		Latency (ms)			Amplitude (μv)				
No.	Age at present	Sex	Dose (mg/kg/day)	Duration (months)	LE	RE	Control*	LE	RE	Inference	Ophthalmological examination	Vigabatrin
1	11y 4m	M	114	85	99	103	105 (8)	16.33	14.06	N	N	Cont
2	10y	M	50	81	125	123	105 (8)	20.0 0	15.73	ABN	ABN	Stop
3	5y 10m	F	50	71	140	135	105 (8)	6.8	7.8	ABN	ABN, RE-OA	Cont
4	9y 10m	F	25	60	127	133	105 (8)	25.11	27.63	ABN	N	Cont
5	5y 4m	M	36	48	No response (previously abnormal)					ABN	ABN	Cont
6	8y 9m	M	25	44	117	127	105 (8)	6.9	5.96	ABN	ABN	Cont
7	4y 7m	F	58.8	43	186	185	105 (8)	9.6	19.5	ABN	N	Cont
8	3y 4m	M	40	40	153	145	105 (8)	11.04	4.97	ABN	N	Cont
9	5y 5m	M	62.5	40	144	149	105 (8)	7.91	6.84	ABN	N	Cont
10	3y 6m	M	50	33	171	167	105 (8)	7.7	4.9	ABN	ABN	Stop
11	3y 3m	M	79.8	34	112	107	105 (8)	11.54	12.05	N	N	Cont
12	19y	F	42	30	200	160	105 (8)	5.10	6.80	ABN	N	Stop
13	2y 10m	F	58	27	111	107	105 (8)	10.3	11.7	N	TS changes	Cont
14	2y 4m	F	111	25	159	0	105 (8)	6.8	0	ABN	N	Cont
15	9y	M	50	24	No response (previously abnormal)					ABN	ABN	Cont
16	2y 3m	F	68	22	189	196	105 (8)	5.6	12.4	ABN	N	Cont
17	2y 2m	M	75	15	203	205	105 (8)	1.2	7.1	ABN	N	Cont
18	4y 7m	M	35	13	137	140	105 (8)	28.3	27.9	ABN	N	Cont
19	1y	M	90	12	133	129	115 (10)	7.1	3.6	ABN	N	Cont
20	1y 2m	M	40	9	113	113	115 (10)	13.1	13.3	N	N	Cont
21	1y 7m	M	62.5	6	104	105	115 (10)	23.4	20.3	N	N	Cont

N, normal; ABN, abnormal; OA, optic atrophy; Cont, continued; VEP, visual evoked potentials; Stop, stopped; LE, left eye; RE, right eye; TS, tuberous sclerosis. *Taylor.[15]

patients over several decades and there are hardly any reports of retinal involvement. In addition, a recent study with ERG comparing patients on VGB and other AEDs found no visual field abnormality in the latter group.[22]

We believe that if ERG had been available in our hospital, retinal involvement could have been picked up earlier. ERG has been found to be more specific in picking up early retinal changes, while EOG has greater sensitivity.[5 7 9 11] Perimetry was found to be sensitive in about 65% of adult patients.[5 10] In our study VEPs were done in 21 patients and abnormalities observed in 16 children, with two having abnormalities even before starting VGB. The actual number of children with abnormal VEP associated with VGB (table 2) was thus 14 of 19 (73.7%). Five had normal VEP.

Our findings of abnormal VEP may be falsely high, as it is possible that a few children with these types of seizures and associated neurological handicaps could have visual pathway abnormalities independent of treatment.

It has been reported that VEP is insensitive in identifying changes as it evaluates the central 10 degrees of the visual field and may miss peripheral dysfunction.[7] Most children on VGB are cases of IS/WS, or other epileptic syndromes. Not only do these patients have refractory seizures, but most also have mental and psychomotor retardation. Such children cannot communicate their visual defects. VGB is better than other AEDs in controlling such seizures effectively,[23] and it continues to be the drug of choice in our treatment protocol for WS.

We consider VGB can be used with caution, subject to baseline VEP, regular eye examinations, and ERG every 3–6 months. If ERG is not available, at least six monthly eye examination is definitely indicated, for which guidelines are available.[24] Simple perimetry, found to be quite sensitive, can be performed only in children with normal intellect. We conclude that treating neurologists must be cautious in using VGB, in deciding whether benefits of seizure control outweigh the risks.

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Pathology of nonaccidental brain injury

It is commonly believed that severely shaken babies have diffuse axonal injury to the brain and that the forces needed to produce such injury are greater than can be explained by shaking alone and imply that the head has also struck a solid surface. Now a detailed neuropathological study (Jennian F Geddes and colleagues. *Brain* 2001;**124**:1290–8 and 1299–306; see also editorial, ibid 1261–2) has suggested that diffuse axonal injury is, in fact, uncommon in these infants and that their diffuse brain damage may be secondary to cervical injury and consequent hypoxia and ischaemia.

They examined the brains of 53 children who had died of presumed nonaccidental brain injury, 37 aged under 1 year ("infants") and 16 aged 13 months to 8 years ("children"). The infants were less likely than the older children to have extracranial injuries but they were more likely to have evidence of previous trauma. Subdural haemorrhage was documented in 43 cases and was recent in 38. Of these 38, however, only four were large enough to cause a volume effect, the remaining 34 being described as trivial ("thin film"). No child under the age of 8 months had a large subdural haemorrhage.

Axonal damage was assessed using immunocytochemistry for β-amyloid precursor protein, a more sensitive method than previous silver stains. Diffuse brain swelling with raised intracranial pressure was considered to be the cause of death in 29 of the 37 infants and 13 of the 16 older children. Microscopic evidence of hypoxia-ischaemia was found in 32 infants and 11 older children, vascular axonal damage in 13 infants and 8 children, and diffuse axonal injury in only two infants and one child.

Eight infants had no signs of head impact and were thought to have been shaken. Seven of these had severe brain swelling and the eighth had severe hypoxic-ischaemic changes after surviving for 5 months. Two of these infants had cervical spinal cord or nerve root damage. The neuropathological findings were similar in these eight infants and the 29 who had evidence of head impact. In all, 11 cases, all infants, had evidence of localised axonal injury at the craniocervical junction or cervical cord. Twenty eight infants and five children had apnoea or cardiorespiratory collapse prior to presentation.

Diffuse axonal injury is uncommon in children who die of nonaccidental brain injury; most have diffuse brain swelling and hypoxic-ischaemic damage.

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