

Ophthalmic Findings in Pediatrics

Peripheral and Central Nervous
System Drugs Advisory Committee

January 7 & 8, 2009

Day 2

Ronald Farkas, M.D. Ph.D.
Division of Neurology Products



Center for Drug Evaluation and Research

Vigabatrin Ophthalmic Adverse Events

- **Day 2**
 - *Emphasis on infants*
 - *Infantile spasms indication*
 - *NDA 22006*
- **Day 1**
 - Emphasis on adults
 - Complex partial seizures indication
 - NDA 20427

FDA Concerns in Adults

(Day 1)

- Vigabatrin visual field constriction
 - Onset and progression variable, unpredictable
 - 1/3rd or more affected after several years
 - about equal proportion mild, moderate, severe
- Damage to central vision may occur
- Uncertain if damage can worsen after stopping

FDA Concerns in Adults

(Day 1)

- Peak incidence of visual damage at \approx 1 year
- Onset at a few weeks or months not rare
- No safe exposure known

Uncertain if infants with IS similar

Infantile Spasms (IS)

Physical Findings

- Peripheral retina
 - Gross atrophy, granular appearance
- Central retina
 - More subtle atrophy, wrinkling in some patients
- Appears *qualitatively* similar to adults

Buncic 2004

Visual Testing

- Perimetry not possible in infants
- Electroretinography (ERG)
 - Most studied objective method to detect retinal injury from vigabatrin
- Little data for other objective methods

Key Questions

- Are ERG results 'true'?
 - If the result is normal, is damage absent?
 - If the result is abnormal, is damage present?
- Is the result clinically useful
 - Help prevent damage...
 - or only diagnose irreversible damage?

ERG Test Performance

- ERG performance as a monitoring test not meaningfully addressed in submission or literature
- Correlation between ERG and vigabatrin retinal damage has been shown, ***but correlation can exist without being strong enough to make a reliable clinical test***

ERG Test Performance

- FDA analysis of ERG performance very limited by lack of data
- Very little data from patients ...
 - with abnormal ERG and damage, confirmed by other method
 - with normal ERG and no damage, confirmed by other methods

IS Data: Toronto Study

- Leading center for pediatric ERG
- Large experience with vigabatrin in IS

Sponsor:

“The best data on prevalence of retinal toxicity in infants with IS”

Toronto Study

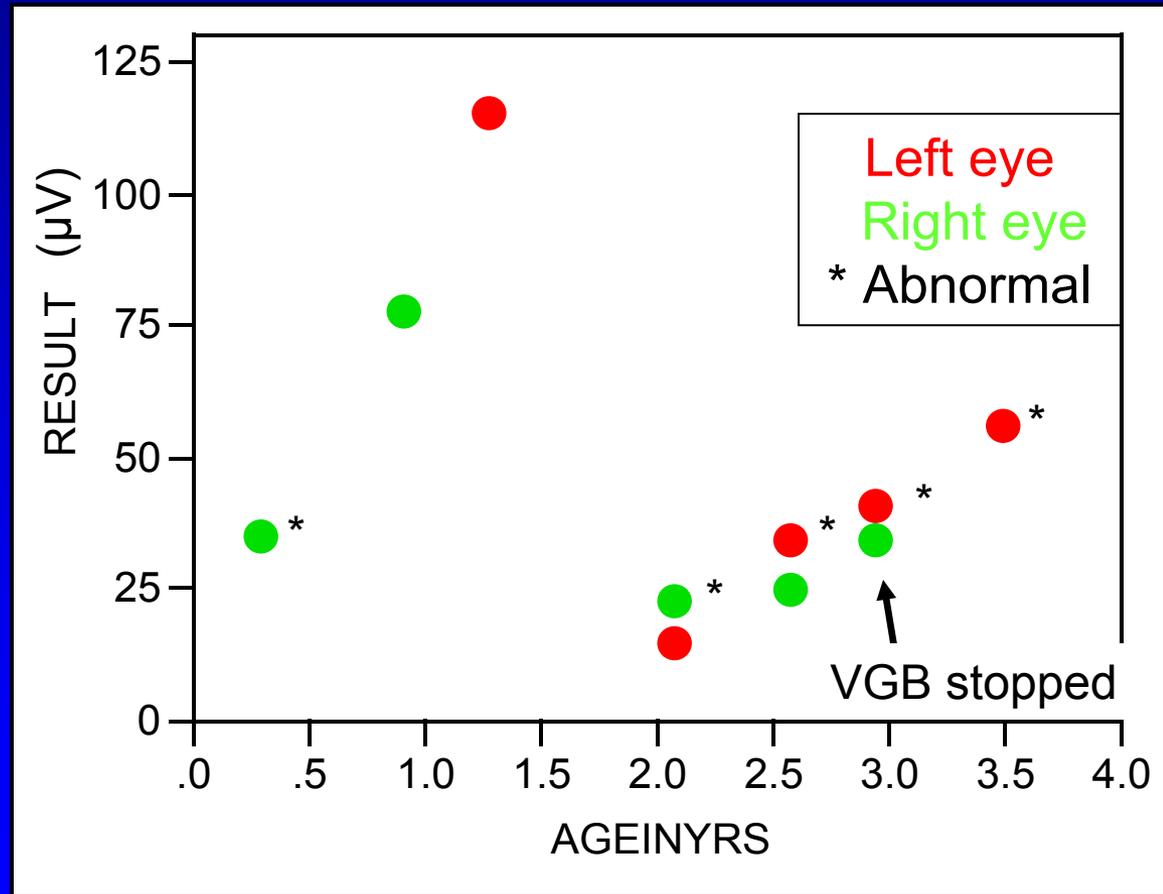
- Prospective arm
 - 117 patients with baseline and ≥ 1 post-baseline exam
- Retrospective arm
 - 89 patients with at least one exam, but no baseline exam

Toronto Study

- Age at most recent ERG \approx 2 years
- Average patient examined 2 to 3 times over 6 to 12 months
- \approx 80% of patients followed 2 years or less

Toronto Study Data

ERG result in microvolts

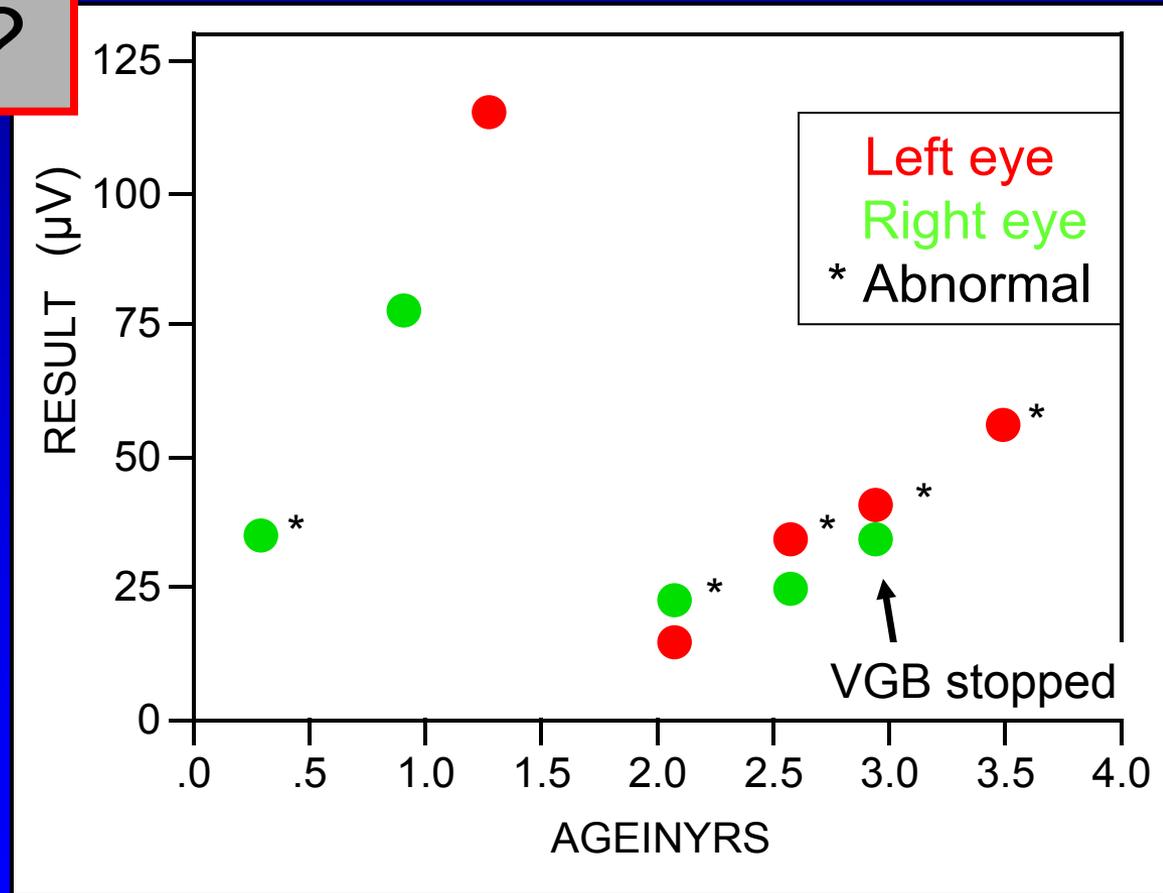


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Toronto Study Data

How interpret?



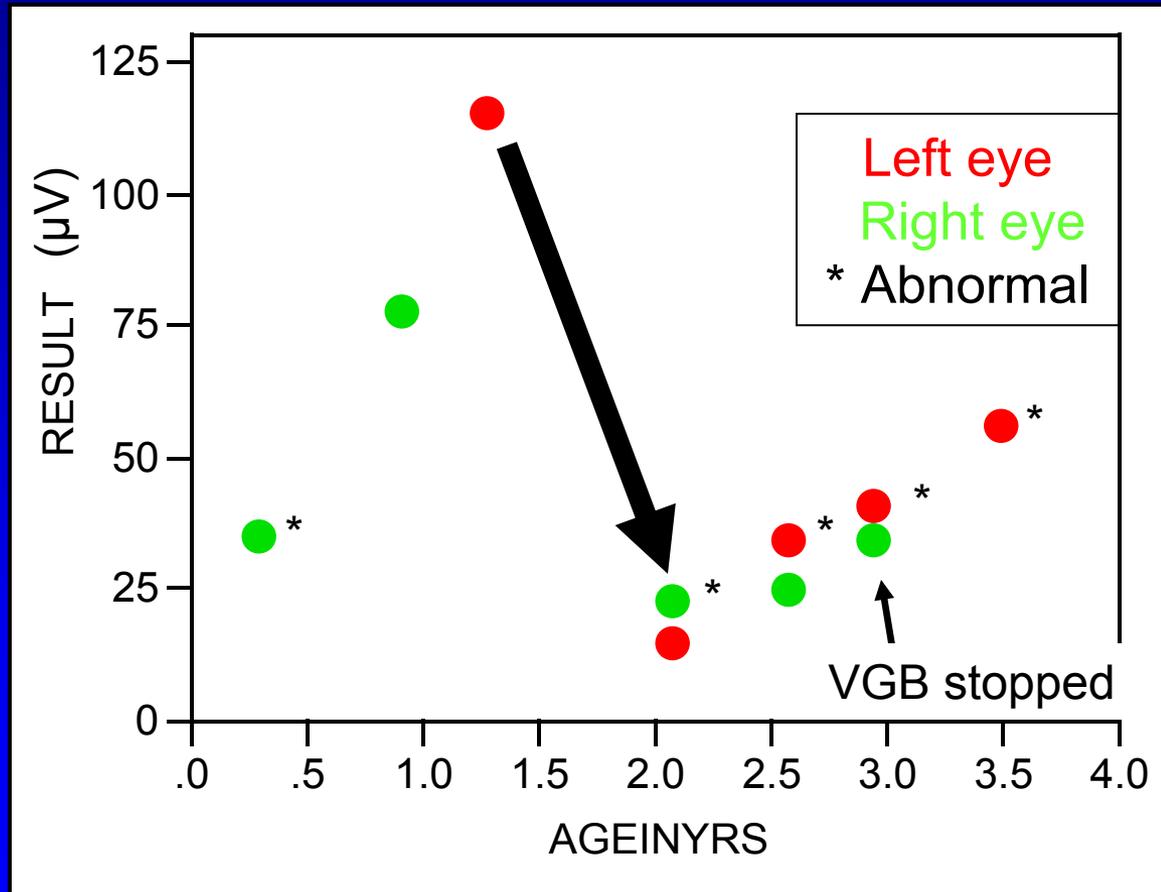
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Perhaps sudden, severe damage?

Maybe ERG can't reliably prevent damage...?

...but is this really vigabatrin damage?

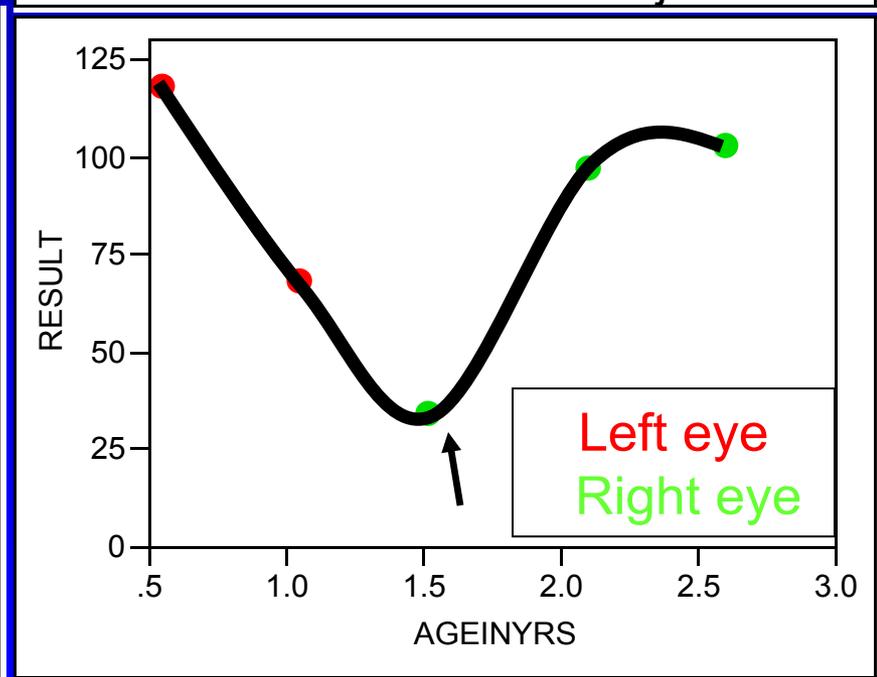
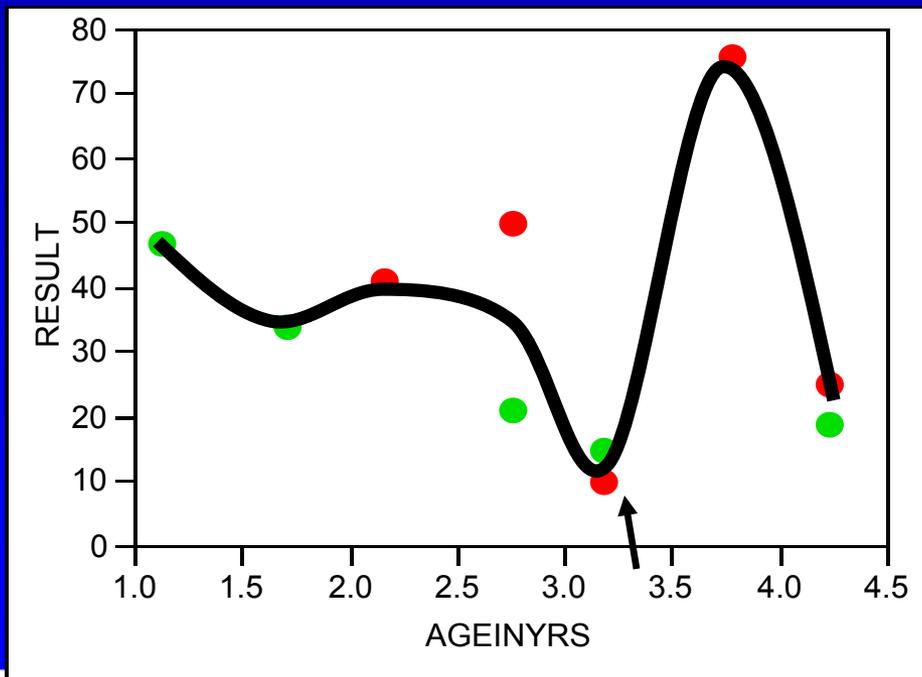
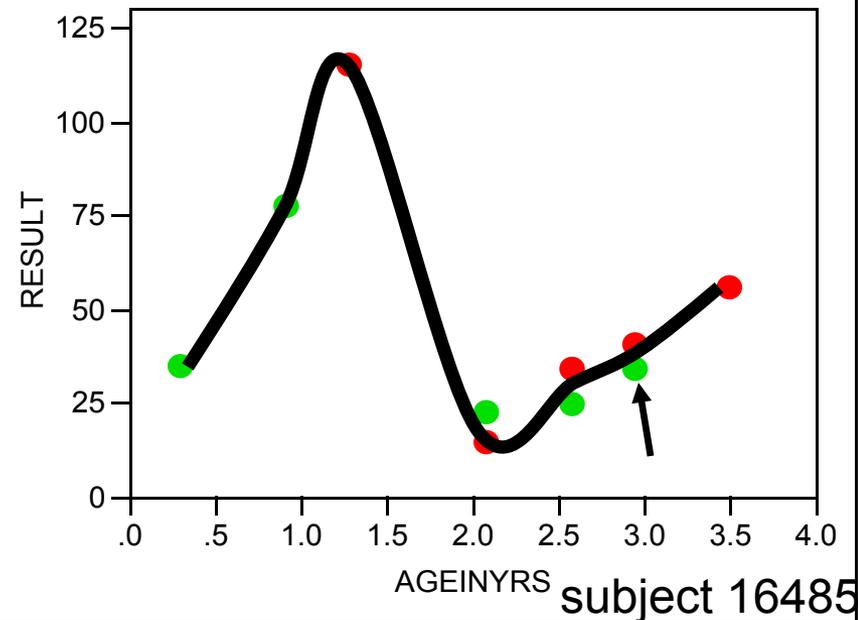


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FDA unable to separate signal from noise in individual ERG data

Arrow = VGB stopped



Subject 15AX2

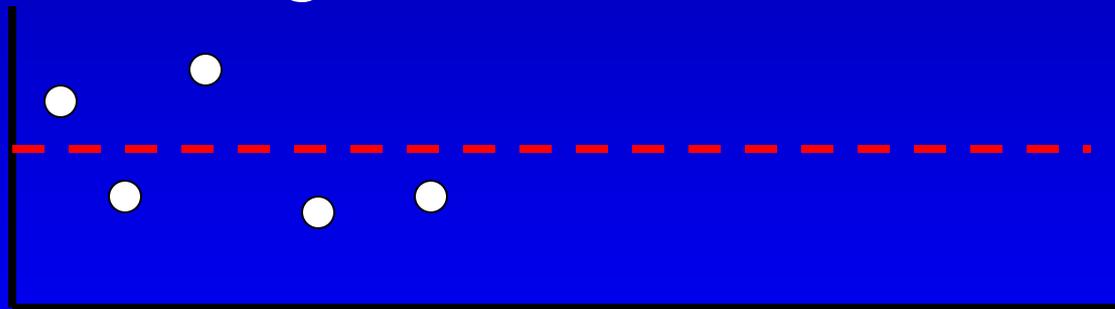
Subject 1528x

- Sponsor conclusions
 - 54% with normal baseline change to abnormal on ≥ 1 subsequent tests
 - 25% 'sustained' abnormal on final 2 exams

How much 'change' due to test variability?

Normal

Abnormal



Similar to coin toss?

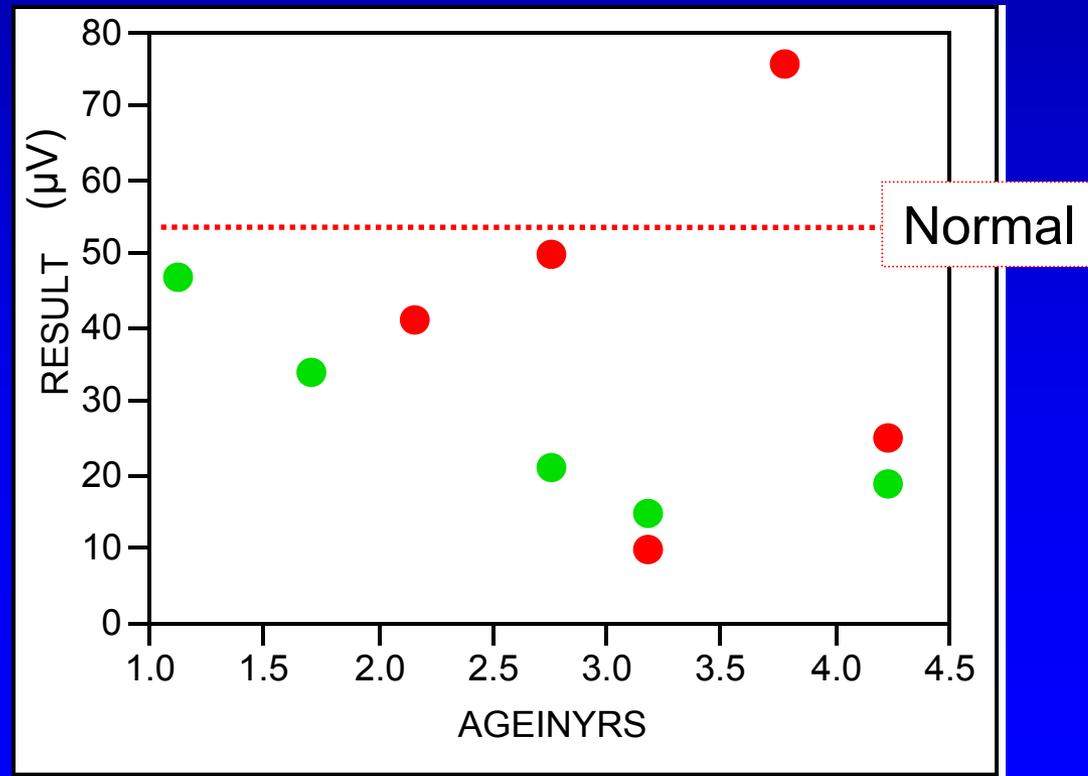
50% heads on first toss

25% heads on both first and second

ERG Endpoint Bias

- 1st post-baseline exam at 6 months
 - By design can't detect damage < 6 months
- Sponsor bases 'abnormal' on 2 tests
 - If 2nd test at 1 year...
 - ...by definition never abnormal till 1 year

- 38% of patients abnormal at baseline
 - Unclear how to monitor these patients
 - Change to 'abnormal' not possible
 - How much lower than low indicates damage?



ERG Sensitivity

By definition, sensitivity is relative to other method

Proportion of patients detected is not informative about number of patients missed (false negatives)

ERG + perimetry in older children and adults may provide estimate of sensitivity in IS

ERG Sensitivity Appears Low in Adults

- Study R003
- Prospective study in adult CPS patients
 - N = 25
- 7 patients (28%) developed field defect
 - 4 mild severity at first diagnosis
 - 3 moderate severity at first diagnosis

ERG Sensitivity Appears Low in Adults

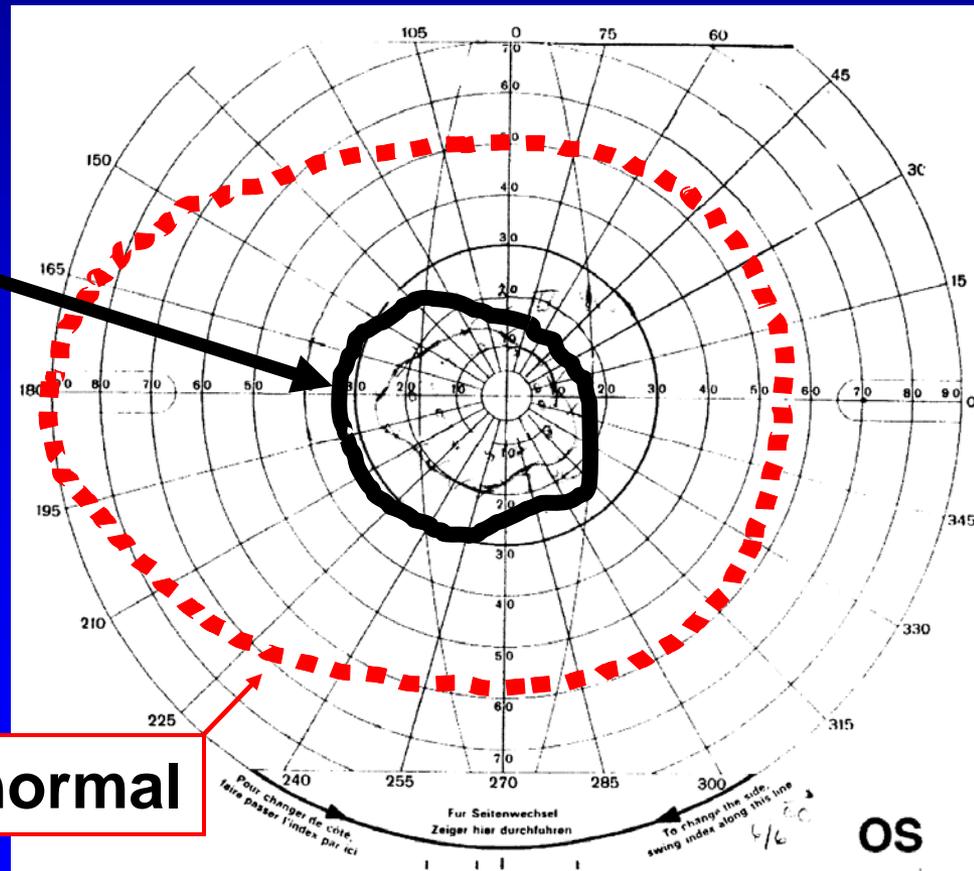
- ERG failed to detect most visual damage
 - None of 4 patients with mild damage
 - 1 of 3 patients with moderate damage

ERG Sensitivity Appears Low in Older Children

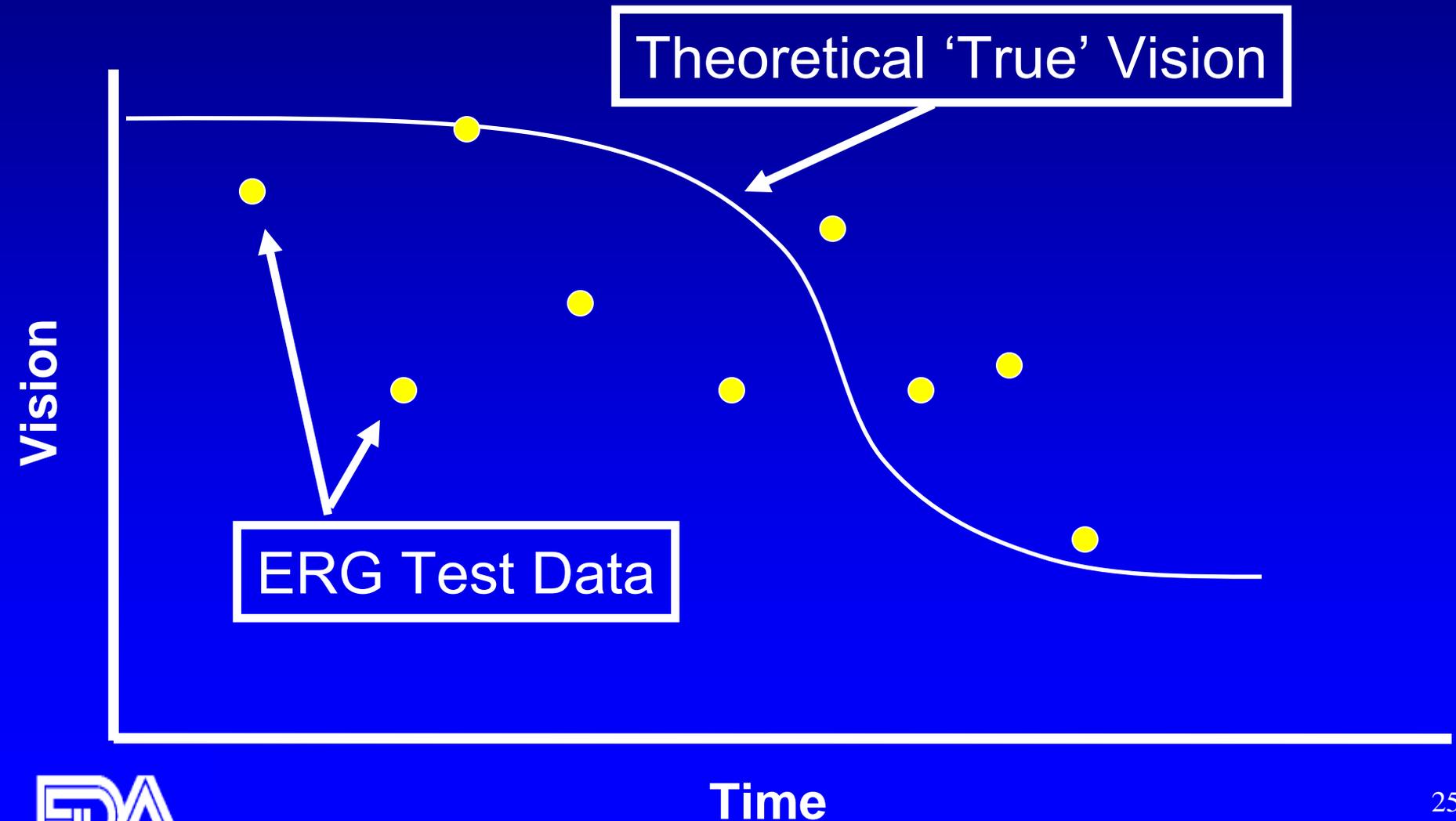
- 10 year old girl, CPS
- 4 years vigabatrin

Severe field constriction

NORMAL ERG

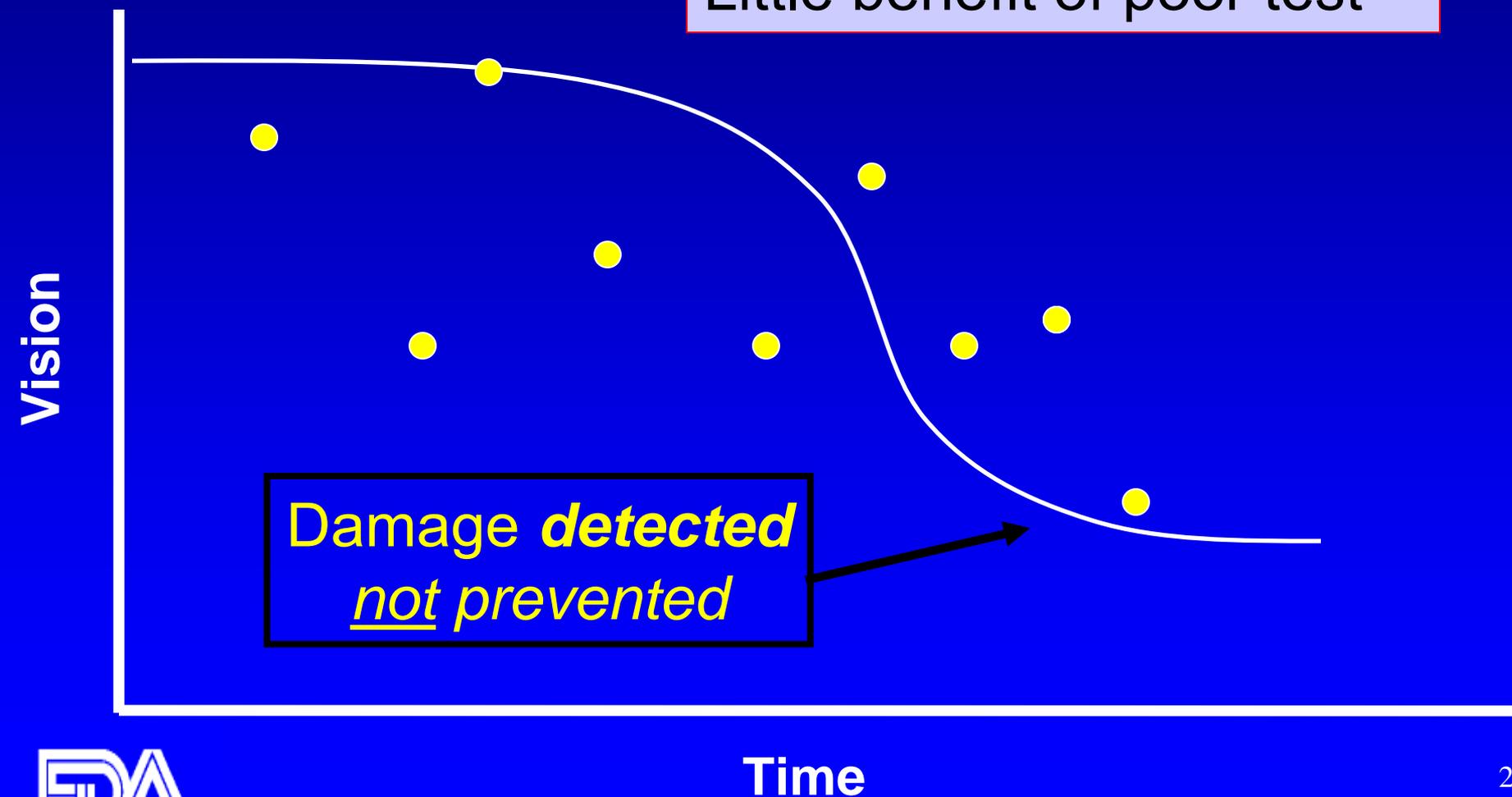


Harder to prevent than detect damage



Harder to prevent than detect damage

Little benefit of poor test



Clinical Consequences of Vigabatrin Vision Damage in Infants with IS

Effects of Vision Damage

- Limited data
 - Case reports
- In adults, may relate to ability to use compensatory strategies, like ‘scanning’
- What is IS patient’s ability to compensate for vision loss?

Vision Damage: Case Report

- 2 ½ year-old boy with trisomy 21
- IS since 9 months
- After 24 months vigabatrin
 - Fundus exam
 - Retinal atrophy involving most of the retina
 - Relatively less involvement of macula
 - Macula showed wrinkling of irregular thickness
 - ERG about 50% below expected
 - Attributed by investigator to vigabatrin

Vision Damage: Case Report

- Acuity in lower half of age-expected normal
- No response to objects in periphery
- Stares straight ahead during testing
- Parents report:
 - Stares straight ahead
 - Responds more to sound than visual cues
 - Parent had to 'attract his attention downward to his food at meal times by tapping on his plate'
- Attributed by investigator to vigabatrin

Summary and Conclusions

Vigabatrin Visual Damage in IS

Summary and Conclusions in IS

- Vigabatrin damage to peripheral and central retinal directly observable in IS
- Observed damage resembles that in adults
 - Severe damage to peripheral retina
 - Less severe damage to central retina

Summary and Conclusions in IS

- Data on visual damage in IS mainly from ERG
- Sensitivity and specificity of ERG for vigabatrin damage may be low
- FDA unable to propose ERG or other testing recommendations

Summary and Conclusions in IS

- Case reports raise concern that visual disability from vigabatrin in some IS patients may be severe
...but question largely unaddressed

Summary and Conclusions in IS

- Weak study design plus questionable ERG data leaves key questions unanswered
 - Severity
 - Frequency
 - Time course and latency of damage
 - Relationship to drug exposure (time and dose)
 - Progression on or off drug