find the characteristic $L_4$-CL deficiency associated with BTHS.

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References

Brain Biopterin and Tyrosine Hydroxylase in Asymptomatic Dopa-Responsive Dystonia
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It is assumed that brain biopterin and dopamine loss should not be as severe in asymptomatic dopa-responsive dystonia caused by GCH1 mutations as it is in symptomatic dopa-responsive dystonia. However, the actual status of dopaminergic systems in asymptomatic cases is unknown. In the autopsied putamen of an asymptomatic GCH1 mutation carrier, we found that brain biopterin loss (~82%) paralleled that reported in dopa-responsive dystonia patients (~84%). However, tyrosine hydroxylase protein and dopamine levels (~52 and ~44%, respectively) were not as severely affected as in symptomatic patients (exceeding ~97 and ~88%, respectively). Our data suggest that the extent of striatal tyrosine hydroxylase protein loss may be critical in determining dopa-responsive dystonia symptomatology.

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Dopa-responsive dystonia (DRD) is a syndrome characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of L-dopa.1,2 Autosomal dominant (AD) DRD can be caused by mutations in the GCH1 gene, which encodes GTP cyclohydrolase I (GTPCH), the first enzyme in the biosynthetic pathway for tetrahydrobiopterin (BH4); the essential cofactor for tyrosine hydroxylase (TH).3,4 Some patients with autosomal recessive DRD have mu-

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tations in the TH gene, and so the two abnormal gene products identified so far in DRD are related to the enzyme TH. 3, 6

Although the loss of enzyme protein was considered to be limited to GTPCH in the AD form of DRD, we found previously that levels not only of total bipterin (BP; most exists as BH4), total neopterin (NP; the by-products of the GTPCH reaction), and dopamine (DA) but also of TH protein in the striatum were reduced in autopsied subjects with GTPCH-deficient DRD. 7, 8 Other DA nerve terminal markers (including dopa decarboxylase [DDC] protein) were preserved in these symptomatic cases. However, the actual status of brain dopaminergic involvement in asymptomatic AD-DRD cases due to incomplete penetrance of GCH1 mutations 9 is unknown. To evaluate possible factors influencing the penetrance, we measured levels of BP, NP, TH, and DDC proteins as well as DA in the autopsied brain of an asymptomatic GCH1 mutation carrier.

Case Report
Family Report
Clinical details of this English-American family with AD-DRD have been reported previously. 10-12 Our subject was a 55-year-old woman who was an asymptomatic carrier of a mutation linked to DRD in this pedigree. 11 Her mother had adult-onset benign parkinsonism (a phenotypic expression of DRD), and her granddaughter developed typical DRD. The asymptomatic carrier had pulmonary fibrosis after chemotherapy and a bone marrow transplant for multiple myeloma. She died after voluntary ventilator termination. A neuropathological investigation of this asymptomatic carrier demonstrated no Lewy bodies and a normal population of cells with reduced melanin in the substantia nigra. There were no degenerative changes in any areas of the brain.

Molecular Genetic and Neurochemical Analysis
This study was approved by the Institutional Review Boards of the East Orange Veterans Affairs Medical Center and the Centre for Addiction and Mental Health. We conducted direct sequencing of GCH1, using genomic DNA from brain tissue. 8 Brain BP and NP levels were determined by high-performance liquid chromatography with fluorescence detection according to the method described by Fukushima and Nixon, 13 with some modifications (using the standards from Schircks Laboratories, Jona, Switzerland). BP includes BH4, quinonoid dihydrobiopterin, and 7,8-dihydrobiopterin. NP consists of degradation products of dihydroneopterin triphosphate, which is synthesized from GTP by GTPCH and then converted into the second intermediate in the biosynthesis of BH4 by 6-pyruvoyltetrahydropterin synthase. NP is generally considered to reflect GTPCH activity. Concentrations of TH and DDC proteins in the striatum were measured by Western blot analysis with affinity-purified rabbit antirat TH and antibovine DDC antibodies. 8 The amount of TH or DDC was calculated by interpolation from a tissue standard curve run on the same gel. Striatal subdivisions were defined anatomically as reported previously. 14 Levels of DA were determined in the intermediate portions of the rostral, intermediate, and caudal subdivisions of the putamen and of the caudate nucleus (see Kish and colleagues 14 for details) by high-performance liquid chromatography with electrochemical detection. 8 For each neurochemical measurement, the ages and postmortem times of 4 to 8 neurologically and psychiatrically normal control subjects were matched closely to those of the asymptomatic carrier. Because there is an influence of immune status on NP concentration, 8 we did not include any control individuals with systemic infectious diseases, conditions in which brain NP levels might have been elevated.

Results
On one allele in the asymptomatic carrier, we identified a G-to-A transition in exon 1 of GCH1 (at nucleotide position 323), resulting in a glycine-to-aspartic acid substitution (Gly 108 Asp). This missense mutation was previously reported in a compound heterozygote for GCH1 mutations; the compound heterozygote developed relatively severe symptoms (dystonia with motor delay). 15 No other mutations in either the coding region or the splice sites of GCH1 were found in the asymptomatic carrier.

Concentrations of brain BP were substantially decreased in the GCH1 mutation carrier compared with those of the age-matched controls (putamen, -82%; caudate nucleus, -82%; frontal cortex, -57%; Table 1). Brain NP levels were also substantially reduced (putamen, -57%; caudate nucleus, -45%; frontal cortex, -68%). Compared with the controls, the asymptomatic carrier had moderate TH protein loss in the putamen (-52%); the magnitude of loss in the caudate nucleus (-30%) was less than that in the putamen. Striatal DDC protein levels were normal in the asymptomatic carrier. Subregional DA concentrations in the striatum of our asymptomatic carrier were within the range of the controls with the exception of those in the intermediate (-43%) and caudal (-44%) subdivisions of the putamen (Table 2).

Discussion
To our knowledge, this is the first report of neurochemical findings in the brain of an asymptomatic GCH1 mutation carrier. The amino acid substitution that resulted from the
BP (pmol/g wet weight)  

| Asymptomatic carrier | Normal control subjects<br>1 | 267 | 198 | 36  
|----------------------|-------------------------------|-----|-----|-----  
|                      | 4<sup>a</sup>                  | 1471 ± 90 | 1101 ± 153 | 84 ± 12  
|                      |                               | (1218–1628) | (686–1404) | (65–119)  

NP (pmol/g wet weight)  

| Asymptomatic carrier | Normal control subjects<br>1 | 29 | 22 | 10  
|----------------------|-------------------------------|-----|-----|-----  
|                      | 4<sup>a</sup>                  | 67 ± 8 | 40 ± 4 | 31 ± 10  
|                      |                               | (49–90) | (30–48) | (17–59)  

TH protein (µg tissue standard/10µg protein)  

| Asymptomatic carrier | Normal control subjects<br>1 | 6.73 | 10.14 | NE  
|----------------------|-------------------------------|-----|------|-----  
|                      | 4<sup>a</sup>                  | 13.91 ± 1.67 | 14.44 ± 0.72 | NE  
|                      |                               | (9.43–17.48) | (12.62–16.14) |   

DDC protein (µg tissue standard/10µg protein)  

| Asymptomatic carrier | Normal control subjects<br>1 | 15.74 | 16.41 | NE  
|----------------------|-------------------------------|-----|------|-----  
|                      | 4<sup>a</sup>                  | 13.58 ± 1.36 | 17.01 ± 1.17 | NE  
|                      |                               | (9.52–15.02) | (14.12–19.43) |   

Table 1. Total Biopterin and Neopterin, Tyrosine Hydroxylase Protein, and Dopa Decarboxylase Protein Levels in the Striatum and Frontal Cortex of an Asymptomatic GCH1 Mutation Carrier and of Normal Control Subjects<sup>a</sup>  

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Subjects</th>
<th>Putamen</th>
<th>Caudate Nucleus</th>
<th>Frontal Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Asymptomatic carrier | 1 | 267 | 198 | 36  
| Normal control subjects<br>1 | 4<sup>a</sup> | 1471 ± 90 | 1101 ± 153 | 84 ± 12  
|                       |                               | (1218–1628) | (686–1404) | (65–119)  
| NP       |                 |        |                |               |  
| Asymptomatic carrier | 1 | 29 | 22 | 10  
| Normal control subjects<br>1 | 4<sup>a</sup> | 67 ± 8 | 40 ± 4 | 31 ± 10  
|                       |                               | (49–90) | (30–48) | (17–59)  
| TH       |                 |        |                |               |  
| Asymptomatic carrier | 1 | 6.73 | 10.14 | NE  
| Normal control subjects<br>1 | 4<sup>a</sup> | 13.91 ± 1.67 | 14.44 ± 0.72 | NE  
|                       |                               | (9.43–17.48) | (12.62–16.14) |   
| DDC      |                 |        |                |               |  
| Asymptomatic carrier | 1 | 15.74 | 16.41 | NE  
| Normal control subjects<br>1 | 4<sup>a</sup> | 13.58 ± 1.36 | 17.01 ± 1.17 | NE  
|                       |                               | (9.52–15.02) | (14.12–19.43) |   

<sup>a</sup>BP, NP, TH protein, and DDC protein levels were measured in the caudal subregion of the putamen and in the intermediate subregion of the caudate nucleus. The age and postmortem time of the asymptomatic carrier were 55 years and 6 hours, respectively.  

<sup>b</sup>Values are expressed as mean ± standard error (range).  

<sup>c</sup>For BP and NP measurements, the ages and postmortem times of the 4 normal control subjects (4 men) were 55 ± 3 (46–59) years and 6 ± 1 (4–8) hours (mean values ± standard error [range]).  

<sup>d</sup>For TH protein and DDC protein measurements, the ages and postmortem times of the 4 normal control subjects (4 men) were 55 ± 3 (46–59) years and 7 ± 1 (5–8) hours (mean values ± standard error [range]).  

BP = total biopterin; NP = total neopterin; TH = tyrosine hydroxylase; DDC = dopa decarboxylase; NE = not examined.  

Table 2. Subregional Levels of Dopamine in the Striatum of an Asymptomatic GCH1 Mutation Carrier and of Normal Control Subjects<sup>a</sup>  

<table>
<thead>
<tr>
<th>DA (ng/mg wet weight)</th>
<th>No. of Subjects</th>
<th>Putamen</th>
<th>Caudate Nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rostral</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Asymptomatic carrier</td>
<td>1</td>
<td>4.19</td>
<td>3.37</td>
</tr>
<tr>
<td>Normal control subjects&lt;br&gt;1</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.83 ± 0.63</td>
<td>5.87 ± 0.57</td>
</tr>
</tbody>
</table>

<sup>a</sup>Subregions in the striatum were defined anatomically as reported previously<sup>14</sup> The age and postmortem time of the asymptomatic carrier were 55 years and 6 hours, respectively, and those of the 8 normal control subjects (1 woman, 7 men) were 57 ± 3 (46–70) years and 9 ± 2 (4–18) hours (mean values ± standard error [range]).  

<sup>b</sup>Values are expressed as mean ± standard error (range).  

DA = dopamine.  

GCH1 mutation present in the asymptomatic carrier (and linked to DRD in this family<sup>11</sup>) affects a highly conserved amino acid residue across species<sup>15</sup>. The mutant allele that has the nonconservative amino acid change most likely produces dysfunctional GTPCH and results in reduced BP and NP. Although it has been assumed that brain GTPCH activity levels are decreased in asymptomatic GCH1 mutation carriers but are still higher than those in GTPCH-deficient DRD patients, our BP and NP data both in the striatum and in the frontal cortex did not distinguish the asymptomatic case (see Table 1) from two symptomatic cases reported previously<sup>8</sup> (BP and NP: putamen, −84 and −62% [mean values]; caudate nucleus, −86% and exceeding −62%; frontal cortex, −62% and exceeding −64%). Such brain pterin results are in agreement with findings that low levels of cerebrospinal fluid BP<sup>12</sup> and lymphoblast NP<sup>16</sup> in asymptomatic carriers were indistinguishable from those in patients with AD-DRD. Ichinose and colleagues<sup>3</sup> reported that GTPCH activity levels in phytohemagglutinin-stimulated mononuclear blood cells were higher in asymptomatic cases (n = 2) than in symptomatic cases (n = 7). However, using cultured lymphoblasts, Bezin and colleagues<sup>16</sup> suggested that the phytohemagglutinin induction alone misrepresents the actual status of GTPCH activity.  

Although striatal DDC protein levels were normal in our asymptomatic carrier and in the reported patients with GTPCH-deficient DRD (consistent with fluoro-
dopa positron emission tomography studies\textsuperscript{10,12}, TH protein concentrations in the putamen were moderately (−52%) and severely (exceeding −97%) reduced in the asymptomatic and symptomatic DRD cases,\textsuperscript{8} respectively (Fig). These human brain findings are compatible with TH protein loss but preserved DDC activity in brains of BH4-deficient mice, that is, GTPCH-deficient \textit{hph-1} mutants and 6-pyruvoyltetrahydropterin synthase gene (PTS) null mutants.\textsuperscript{17,18} These data suggest that striatal DA reduction in GTPCH-deficient DRD is caused not only by decreased TH activity resulting from a low cofactor level but also by actual loss of TH protein without nerve terminal loss. We previously speculated that low levels of TH protein in the striatum, especially in the putamen, of GTPCH-deficient DRD were caused by a diminished regulatory effect of its cofactor, BH4, on the steady-state level (stability/expression) of this enzyme protein.\textsuperscript{2,8} In fact, gene-transfer experiments have suggested that the coexpression of GTPCH with TH stabilizes TH protein in vivo.\textsuperscript{17} Because TH protein concentrations in the substantia nigra (where striatal TH molecules are synthesized) were normal in the GTPCH-deficient DRD patients, BH4 could control stability rather than the expression of TH molecules.\textsuperscript{2,8} This is supported by a recent report showing loss of TH protein but not of TH mRNA in the brains of BH4-deficient PTS knockout mice.\textsuperscript{18} Alternatively, there might be a dysfunction of TH protein transport from the substantia nigra to the striatum due to congenital partial GTPCH deficiency. The exact mechanism by which striatal TH protein decreases in the AD form of DRD is unclear. However, the different degrees of TH protein loss in the putamen between asymptomatic and symptomatic GTPCH-deficient DRD cases with the same magnitude of striatal BP and NP reduction (see Fig) suggest that there are additional genetic or environmental factors, or both, that may modulate a regulatory effect of BH4 on the steady-state level of TH molecules.

Finally, consistent with other postmortem brain data suggesting that greater than 60 to 80% of striatal DA loss is necessary for clinically overt motor symptoms to occur,\textsuperscript{20} the maximal 44% reduction of DA in the striatum of our \textit{GCH1} mutation carrier (see Table 2) was not sufficient to produce any DRD symptoms. In the asymptomatic carrier, the DA reduction in the caudal subregion of the putamen (−44%), which is most affected by DA loss in patients with Parkinson’s disease,\textsuperscript{14,20} was much milder than that (−88%) in the reported DRD patients\textsuperscript{8} (see Fig).

In conclusion, although our findings in a single case require replication in a representative number of subjects, only a modest reduction of TH protein despite a marked reduction of BP in the putamen of our asymptomatic \textit{GCH1} mutation carrier suggests that the extent of striatal TH protein loss may contribute to gender-related incomplete penetrance of \textit{GCH1} mutations in the AD form of DRD.

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We thank Linda DiStefano for her technical assistance.

References


Seizure-Associated Hippocampal Volume Loss: A Longitudinal Magnetic Resonance Study of Temporal Lobe Epilepsy

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This longitudinal quantitative magnetic resonance imaging study of 24 patients with mild temporal lobe epilepsy shows an ipsilateral hippocampal volume decrease of 9% (range, −30 to +0.5%; \( p = 0.002 \), paired \( t \) test) over a period of 3.5 ± 0.7 years. The hippocampal volume loss was correlated to the number of generalized seizures between the scans (\( p = 0.0007 , r = 0.6 \)), suggesting seizure-associated hippocampal damage.

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There is controversy over whether seizures cause damage to the brain. Animal studies strongly suggest that even single seizures are harmful.1 In humans, seizure-associated damage is difficult to prove because the controlled conditions of an animal experiment are not fulfilled. Seizure-associated damage may be reflected in volume loss. Volumetric changes have been extensively studied in temporal lobe epilepsy (TLE). In TLE, magnetic resonance imaging (MRI) and pathological studies suggest that hippocampal volume (HCV) loss may be the result of two potential sources of damage: first, that induced by an early event such as a prolonged febrile convulsion, and second, damage associated with seizures themselves.2,3 Some retrospective quantitative MRI studies have suggested progression of hippocampal atrophy, correlating with the frequency of generalized seizures,4,3 whereas other studies have not.5

To disentangle the effects of an initial injury from damage secondary to seizures themselves, prospective studies are necessary. In this study, we used consecutive quantitative magnetic resonance imaging to assess hippocampal atrophy in patients with TLE. Each patient had at least one clinical seizure and epilepsy surgery planned. MRI scans were obtained at baseline and 3.5 ± 0.7 years later. We found a significant decrease in the ipsilateral HCV (9%; \( p = 0.002 \), paired \( t \) test) over a period of 3.5 ± 0.7 years. The decrease was correlated with the number of generalized seizures (\( r = 0.6 \)).

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studies are needed. Prospective MR studies have documented the development of hippocampal sclerosis (HS)\(^6\)–\(^8\) after a severe initial injury. Seizure-associated damage has only rarely been investigated prospectively.\(^9\)

We prospectively followed newly diagnosed adult TLE patients with normal MRI findings on their first scan. These patients rarely progress to intractable TLE with HS\(^10\), but they uniquely allow us to study the effects of seizures on an MRI normal hippocampus.

Patients and Methods

Patients

Thirty-four consecutive patients with newly diagnosed lateralized TLE, evaluated at our First Seizure Clinic, were enrolled in the study. Diagnosis was based on clinical history, seizure description, and electroencephalogram (EEG) findings.\(^11\) All patients had a routine EEG within 24 hours and, when it was normal, a sleep-deprived EEG.\(^12\) A special effort was made to get a seizure description by an eyewitness. All patients had at least two recurrent seizures within 4 months. The diagnosis of TLE was based on typical temporal auras and/or EEG discharges with a maximum over the temporal lobes. Lateralization was based on lateralized EEG discharges, with or without lateralized seizure features. Epileptiform discharges were diagnosed in the presence of focal spikes or sharp waves followed by slow waves. Only patients with normal MRI findings reported on their clinical study were included. Most patients were seen every 2 to 6 months during the follow-up period (M.A.K.).

After 3 to 4 years, these 34 patients were invited for a second MRI. Five did not wish to participate, 4 would have required sedation for scanning, and 1 suffered from another intercurrent disease; therefore, 24 patients were rescanned. Dates and circumstances of each generalized tonic clonic seizure (GTCS) and antiepileptic treatment between the two scans were obtained from clinical notes and confirmed by interview. We believed that our counts of complex partial seizures were not accurate enough to be included as a variable.

Magnetic Resonance Examination

The first MRI was performed on a 1.5T Siemens SP Magnetom scanner, and the second was performed on a 1.5T GE scanner. The hippocampal structure was assessed with the same protocol at both scanners.\(^13\) For HCV measurements, three-dimensional coronal acquisition was used (Magnetization-Prepared Rapid Acquisition Gradient Echo for the first MRI and Fast Spoiled Gradient Echo for the second).

The measurement of HCV was based on our established protocol.\(^13\) Measurements were performed twice (by R.S.B.) in separate sessions, without an awareness of the number of GTCSs. The variability between measurements of the same scan was 3% (SD, 6). Limits of agreement (mean difference ± (2 × standard deviation))\(^14\) were between +357 and −248 mm\(^3\). All HCVs were corrected for the total of both hemicranial volumes\(^13\) without gender correction. The mean of the two corrected measurements was used.

Statistics

A paired t test was used for the individual volume change between the scans. Simple regression analysis was used for the correlation between the volume change (expressed as a percentage) and the number of GTCSs between the scans (the correlation coefficient is indicated). A post hoc analysis on possible predictors for a mild course (less than two GTCSs between scans) was performed with post hoc analysis of variance tests corrected for multiple comparisons (Bonferroni correction). The level of significance was set at 5%.

Results

Clinical Findings

The 24 patients (13 females and 11 males) were 30 ± 14 years at the epilepsy onset. Seven had right-sided TLE, and 17 had left-sided TLE. Seizure onset was between 1 month and 17 years before the first scan (mean, 3.6 years). These early seizures consisted mainly of unrecognized simple partial seizures. At the time of the first scan, they had experienced between 0 and 5 (mean, 1.5) GTCSs. Fifteen patients were treated with carbamazepine, 3 received other drugs, and the remaining 6 patients were untreated.

The second MRI was performed 3.5 ± 0.7 years after the first. During this period, the patients had a further 0 to 8 (mean, 1.7) GTCSs. Fifteen patients had a mild course (0–1 GTCSs), whereas 9 had two or more seizures (Table). At the time of the second scan, 10 of the 24 patients were treated with carbamazepine, 5 received other drugs, 7 were untreated, and 2 more patients were on a combination therapy of two antiepileptic drugs.

Magnetic Resonance Imaging Findings

In 1 of the 24 patients, qualitative and quantitative assessment showed normal findings at the initial investigation and unilateral HS (qualitatively defined as volume loss, increased signal, and disturbed internal architecture) at the second investigation.\(^15\) In the other 23 patients, the qualitative assessment of the hippocampi was normal on both scans.

The mean ipsilateral HCV was 3,234 mm\(^3\) (SD, 455) at the first scan and 2,967 mm\(^3\) (SD, 539) at the second scan. The mean contralateral HCV was 3,297 mm\(^3\) (SD, 466) at the first scan and 3,140 mm\(^3\) (SD, 473) at the second scan. Between the first and second scans, the corrected, individual ipsilateral HCV decreased by 9% or 267 mm\(^3\) (range, decrease of 30% to increase of 0.5%; p = 0.002, paired t test). The contralateral HCV decreased by 5% or 157 mm\(^3\) (range, decrease of 17% to increase of 6%, not significant).

The ipsilateral HCV loss correlated with the number of GTCSs between the scans (p = 0.0007, r = 0.6; Fig). After exclusion of the HS patient, the remaining patients still showed a correlation between GTCSs and...
ipsilateral HCV loss \( (p = 0.009, r = 0.5) \). Ipsilateral HCV loss was not associated with the number of GTCSs before the first scan, age at onset, age at investigation, gender, or a positive family history of epilepsy.

All patients with a mild course showed ipsilateral HCV loss of less than 15%. These patients were older at the onset of their epilepsy (mean, 34; SD, 15 years) than those with a more severe course (mean, 21; SD, 9 years; \( p = 0.02 \); see Table). Treatment with antiepileptic drugs was not different between those with mild or more severe courses. However, a combination of two drugs was only used in 2 patients with a more severe course (one with three GTCSs and an HS patient with six GTCSs). The correlation between GTCSs and ipsilateral HCV loss was still significant after the exclusion of these 2 patients \( (p = 0.01, r = 0.5) \).

### Discussion

This prospective, longitudinal quantitative MR study shows that patients with a diagnosis of lateralized TLE as adults have a small ipsilateral HCV decrease associated with the number of GTCSs experienced between the scans. Only 1 of 24 patients developed HS during the observation period. The rarity of progression into HS in adults is in agreement with previous reports. The majority of adult, newly diagnosed TLE patients have a mild course with rare seizures. In this patient group, the exact number of GTCSs can be determined relatively easily, and the disease is recognized not long before the patient is first investigated. The follow-up period of 3.5 years on average may be at the lower limit that allows a sufficient number of seizures.