Published in final edited form as:

Epilepsy Res. 2016 November ; 127: 66–71. doi:10.1016/j.eplepsyres.2016.08.003.

Anti-mullerian hormone is higher in seizure-free women with epilepsy compared to those with ongoing seizures

Cynthia L. Harden, MD^{a,*}, Page B. Pennell^b, Jacqueline A. French^c, Anne Davis^d, Connie Lau^e, Nichelle Llewellyn^b, Benjamin Kaufman^c, Emilia Bagiella^a, and Ariel Kirshenbaum^b

^aIcahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY, 11029, USA

^bBrigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA, 02115, USA

^cNYU School of Medicine, 462 1st Avenue, New York, NY, 10016, USA

^dColumbia University Medical Center, 630 W 168th St, New York, NY, 10032, USA

^eNorthwell Health, 611 Northern Boulevard, Great Neck, NY, 11021, USA

Abstract

Objective: To determine if anti-mullerian hormone (AMH), a neuroactive peptide hormone and a measure of ovarian reserve, is different between women with epilepsy (WWE) and healthy controls (HC) seeking pregnancy and to evaluate epilepsy-related factors associated with AMH concentrations.

Methods: Subjects were participants in Women with Epilepsy: Pregnancy Outcomes and Deliveries (WEPOD), a multi-center prospective, observational cohort study evaluating fecundity in WWE compared to HC, ages 18–40 years. WWE were divided into a Sz+ group or a Sz– group, dependent on whether they had seizures within the 9 months prior to enrollment. Serum was collected, and AMH concentrations were measured as an exploratory analysis. Linear and logistic regression models were used to assess associations and control for covariates.

Results: Serum AMH concentrations were measured in 72 out of 90 enrolled WWE and 97 out of 109 HC; the remaining subjects became pregnant before serum was obtained. Thirty WWE were in the Sz+ group and 40 in the Sz– group (retrospective seizure information was missing for two). All AMH concentrations were within the range, however, the normal inverse correlation between age and AMH was present in the HC and in the Sz– groups, but was lacking in the Sz+ group. Mean AMH concentration was higher in the Sz– group (3982 pg/ml (SD +/-2452)) compared to the Sz+ group of WWE (2776 pg/ml (SD +/-2308)) and HCs (3241 (SD ± 2647)). All values were within the expected range for age. In WWE, by linear regression, after controlling for age and BMI, seizure occurrence remained associated with AMH ($p = 0.025$). In the prospective phase of the study, AMH concentrations were also associated with seizure occurrence

*Corresponding author at: Mount Sinai Beth Israel Phillips Ambulatory Care Center, 10 Union Square East, Suite 5D, New York, NY, 10003, USA.

Disclosures of conflict of interest

Author Jacqueline A. French, MD is Chief Scientific Officer of the Epilepsy Foundation and received salary support for such. The remaining authors have no conflicts of interest.

during the menstrual cycle in which the serum sample was obtained ($p = 0.012$). Antiepileptic drugs and other epilepsy factors were not associated with AMH concentrations. When analyzing the Sz- WWE group and the HC group by linear regression with AMH as the dependent variable, after controlling for age and BMI, the association with AMH was also present ($p = 0.017$). AMH concentrations of the Sz+ group and HCs did not differ.

Significance: In this exploratory analysis, seizure freedom was associated with higher AMH concentrations compared to women with ongoing seizures and to HCs. Future studies should further investigate the mechanism of the association of AMH with seizure occurrence, whether AMH could have a direct seizure-protective neuroactive hormone effect, as well as implications of AMH concentrations as a biomarker for ovarian reserve in women with epilepsy.

Keywords

Seizures; Anti-mullerian hormone; AMH; Epilepsy; Ovarian reserve

1. Introduction

The Women with Epilepsy: Pregnancy Outcomes and Deliveries (WEPOD) study is a multi-center prospective, observational cohort study evaluating fecundity in women with epilepsy (WWE) compared to healthy controls (HCs) as they progress from attempting conception through pregnancy and delivery. A prespecified secondary aim of the study was to evaluate the associations between hormones, antiepileptic drugs (AEDs) and seizures. In keeping with this aim, we compared anti-mullerian hormone (AMH) concentrations in serum samples collected during the study. Our objective was to explore the effects of epilepsy factors on AMH concentrations.

AMH is a measure of acyclic ovarian activity (Karkanaki et al., 2011) and is used clinically to predict response to in vitro fertilization treatments (Practice Committee for the American Society of Reproductive Medicine, 2015). In females, AMH production by the granulosa cells of small ovarian follicles begins before birth, declines in young adulthood and is nearly undetectable by menopause. The action of AMH is to limit initiation of small antral follicle growth prior to selection of a dominant follicle for ovulation. AMH varies little across the menstrual cycle. Age is the most important determinant of AMH, but concentrations may also be influenced by body mass index, and the presence of polycystic ovarian syndrome in which it is increased (Karkanaki et al., 2011). AMH drops precipitously with ovarian damage following radiation or chemotherapy (Visser et al., 2006).

AMH is a member of the transforming growth factor-beta (TGF-beta) family and has receptors in brain tissue, including the hippocampus (Cimino et al., 2015; Lebeurrier et al., 2008). It is highly neurophysiologically active and protects neurons against N-methyl-D-aspartate (NMDA)- mediated neuronal injury in both in vitro and in vivo models (Lebeurrier et al., 2008). Therefore, AMH is a neuroactive peptide hormone, and has the potential to influence seizure occurrence, as well as serve as a biomarker for reproductive dysfunction in women with epilepsy.

The presence of reproductive dysfunction in women with epilepsy is supported by reports of lower birth rates, earlier onset of perimenopause and menopause and a higher incidence of polycystic ovary syndrome (PCOS) compared to the general population of women (Harden and Pennell, 2013; Harden et al., 2003). A proposed mechanism of endocrine disruption is via abnormal neurophysiologic activity through disruption of rhythmic hypothalamic gonadotropin-releasing hormone (GnRH) production and downstream irregular luteinizing hormone (LH) secretion from the pituitary gland (Quigg et al., 2006; Meo et al., 1993; Herzog et al., 2003).

This cross-sectional exploratory study is the first report of AMH in women with epilepsy including a comparator healthy control group and provides preliminary evidence for development of these hypotheses. Since the AMH evaluation was exploratory, there was no a priori hypothesis upon which to derive a sample size; the WEPOD study was powered to detect a difference in fecundity across WWE and HCs prospectively trying to achieve pregnancy for 1 year.

2. Methods

The inclusion criteria for both groups in the WEPOD study were age 18–40 years, a current male partner and having discontinued all forms of birth control within the past six months to achieve pregnancy. The WWE group also had to have well-documented epilepsy, determined by history, electroencephalography and imaging results. Exclusion criteria for both groups included: 1) smoking more than 10 cigarettes/day, 2) a diagnosis of severe endometriosis, 3) a history PCOS, high prolactin or nipple discharge, untreated thyroid disease, pelvic radiation or past exposure to chemotherapy 4) past, unsuccessful attempts to achieve pregnancy for at least a year, 5) a partner with impaired fertility, 6) use of medroxyprogesterone acetate injectable suspension within the previous six months, and 7) planned use of medications to enhance fertility. This study was approved by the institutional review board at each site, and women were enrolled in the study from October 2010 until March 2014. The WWE were recruited from the epilepsy outpatient clinics at each site, and HC were recruited through public outreach including posting flyers, emails, newspaper and online announcements. All subjects were enrolled after informed consent was obtained.

Reproductive, general, medication and health histories were obtained in both groups. A detailed epilepsy history was obtained in the WWE group. WWE were asked to recall the total number of seizures in the nine months prior to enrollment. This epoch was chosen to provide a comparison of the historical estimate of seizure frequency of the nine months before the period of pregnancy which was anticipated to follow prospectively within the study. WWE were then divided into two groups, those who reported seizures in the prior 9 months designated as Sz+ and those without seizures designated as Sz-. Epilepsy characteristics captured included seizure type, which was captured in 4 mutually exclusive categories as follows: 1) Generalized tonic clonic seizures 2) Focal seizures 3) both 4) unspecified. Current antiepileptic drug (AED) use was captured, categorized further as monotherapy or polytherapy and if AEDs were hepatic enzyme-inducers. The following AEDs were categorized as strong hepatic enzyme inducers: phenobarbital, primidone, carbamazepine, phenytoin and oxcarbazepine. All other AEDs were not categorized as

strong inducers. Participants recorded seizures prospectively and daily via an electronic seizure diary after study enrollment.

2.1. AMH specimens

Serum samples were collected from study subjects after enrollment and prior to conception when possible. Blood draws occurred during scheduled daytime study visits. Blood samples were centrifuged at room temperature and serum was transferred to cryovials and immediately stored at -20°C . All samples were transferred within three months to long-term storage in a -80°C freezer on site at Harvard, following shipment overnight on dry ice as batched groups if collected from another site. The AMH assay was performed in the laboratory of the Harvard Catalyst Clinical Research Center (HCCRC) as part of their batch sample analysis program, utilizing the picoAMH Anti-Mullerian hormone-enzyme linked immunosorbent assay (ELISA) kit (Ansh Labs, Webster, TX).

2.2. Statistical Analysis

AMH concentrations were square-root transformed to normalize the values and stabilize the variance. Univariate comparisons were conducted using one-way ANOVA, chi-square, Spearman's, Pearson's and partial correlations. Linear and logistic regression models were used to control for important covariates, described above, which were age and BMI. All analyses were conducted using a 2-tailed 0.05 level of significance.

3. Results

AMH concentrations were obtained in 72 out of 90 enrolled WWE (80%) and 97 out of 109 control women without epilepsy (89%). Concentrations were not obtained in 18 WWE and 12 HC because they achieved pregnancy before the time of blood drawing. Historical seizure occurrence was not available for two WWE, therefore the following analyses were carried out on 70 WWE and 97 HC.

Age of the WWE ranged from 24 to 40 years with a median of 32, and for the control group ranged from 23 to 40 years with a median of 31. There was no difference across groups with respect to age, BMI or ethnicity, however there was a greater proportion of white women in the WWE group compared to the HC group (87% vs. 57%, chi-square 20.86, $p < 0.05$).

Of the 70 WWE, 53 reported a history of generalized tonic-clonic convulsions (GTCs), 32 were treated with lamotrigine (LTG) monotherapy and 17 with levetiracetam (LVT) monotherapy. Eight were treated with polytherapy and 14 with at least one hepatic enzyme-inducing AEDs. Forty women reported no seizures in the 9 months prior to enrollment. Of the remaining 30 women, the total number of seizures in the nine months prior to enrollment ranged from 1 to 306 seizures with a median of 4.5. Age, BMI, race or ethnicity did not associate with reported seizure occurrence in the nine months prior to enrollment.

AMH correlated with age in the Sz- group, (Pearson's correlation -0.453 , $p = 0.003$) as well as in HCs (Pearson's correlation -0.374 , $p < 0.0001$). AMH did not correlate with age in the Sz+ group (Pearson's correlation 0.074 , $p = 0.699$) (see Fig. 1). Across the entire cohort, BMI was inversely correlated with AMH concentrations (Pearson's correlation

–0.160; $p = 0.040$). Age and BMI did not correlate (Pearson's correlation –0.012; $p = 0.868$). There was no difference in AMH concentrations across ethnicity (Hispanic vs not Hispanic) ($p = 0.749$) or race ($p = 0.543$) utilizing one-way ANOVA.

In WWE, there was no correlation between AMH and age of onset of epilepsy with both as continuous variables, and history of GTCs, seizure type (generalized vs focal), use of lamotrigine or levetiracetam monotherapy, (most frequently used monotherapies), monotherapy vs. polytherapy, or the use of strongly inducing AEDs, each evaluated as categorical variables.

The mean AMH value was 2776 pg/ml (SD $\pm$ 2308) for the Sz+ group, 3982 pg/ml (SD $\pm$ 2452) for the Sz– and 3241 pg/ml (SD $\pm$ 2647). for HCs (see Table 1 for demographic, seizure and epilepsy factors and AMH concentrations across the three groups). Within the group of WWE, when analyzed by linear regression with AMH square root as the dependent variable, after controlling for age and BMI, seizure occurrence remained associated with AMH ($p = 0.025$); the Sz– group had with higher AMH concentrations. When analyzing the Sz– group and HCs by linear regression with AMH square root as the dependent variable, after controlling for age and BMI, the association with AMH was also present ($p = 0.017$), with higher AMH concentrations present in the Sz– group. There was no association with AMH across the groups of Sz+ and HCs.

In the prospective phase of the study, seizure freedom during the menstrual cycle in which the AMH serum sample was obtained also was associated with higher AMH concentrations by linear regression ($p = 0.012$).

Within the subjects who had seizures, AMH was analyzed according to seizure type. Subjects reported seizure types in the following proportions: 1) Generalized tonic clonic seizures in 30% of subjects 2) Focal seizures in 63% of subjects 3) both in 1% of subjects 4) unspecified in 4% of subjects, with one subject missing this data. AMH across generalized and focal seizure types were compared, since these comprised the majority of seizure categories reported. There was no difference in AMH when comparing these two seizure types in the 9 month historical period (generalized AMH 2189 pg/ml $\pm$ 1541 and focal, AMH 3212 pg/ml $\pm$ 2674 ($p = 0.254$)) and in the prospective period (generalized AMH 2105 pg/ml $\pm$ 1890 and AMH 3058 pg/ml $\pm$ 2252 ($p = 0.332$)). For lifetime seizure occurrence (outside of these two study epochs), there was also no difference in AMH across seizure types. the AMH in subjects who reported only generalized seizures over their lifetime was 3953 pg/ml $\pm$ 2804 and for subjects with only focal seizures over their lifetime was 3338 pg/ml $\pm$ 2290 ($p = 0.393$).

In order to explore the possibility that subtle undiagnosed polycystic ovary disease could be a contributor to higher AMH concentrations in the Sz– group compared to the other groups, testosterone concentrations, BMI and ovulation rates for one menstrual cycle per group were each evaluated as the dependent variable across the three groups additionally controlling for age. Using linear regression, there was no association with testosterone concentrations ($p = 0.741$) or BMI ($p = 0.519$) or for ovulation rates (by logistic regression $p = 0.065$) across the three groups. There were more anovulatory cycles for HC than for WWE. The testosterone

concentrations were not different across the three groups with mean testosterone levels as follows: Sz- = 29.6 ng/dL $\pm$ 9.6, Sz+ = 29.3 ng/dL $\pm$ 10.0, HC = 29.3 ng/dL $\pm$ 13.0. However, the expected correlation between AMH and testosterone, controlling for age (Koutlaki et al., 2013), was present in the HC control group (partial correlation 0.236, p = 0.021) but not in the WWE group (partial correlation -0.044, p = 0.718).

There was a significant inverse association between the total number of seizures occurring in the 9 months prior to enrollment and AMH concentrations (Spearman's ρ = -0.302, p = 0.011) analyzing all subjects including those with no seizures. However, the number of seizures in the 9 months before study enrollment was not associated with AMH in the linear regression model after controlling for age and BMI.

None of the HC and eight of the WWE had an AMH concentration of less than 1000 pg/ml. This cut-off for AMH concentration is below the tenth percentile for the study age group (7). Seven of these subjects were in the Sz+ group, and comprised approximately one fourth of the total group women who had seizures (n = 30), while only one of the Sz- group had an AMH concentration of less than 1000 pg/ml. AMH concentrations of less than 1000 pg/ml were associated with the Sz+ group (p = 0.013 by logistic regression).

4. Discussion

This exploratory report reveals two findings regarding AMH in women with epilepsy, both of which are hypothesis-generating. The first finding, evidenced by the disassociation between age and AMH in the Sz+ group as well as the relatively lower AMH concentrations of this group within the study cohort, suggests that seizures are reproductive endocrine disruptors. No other seizure factors including seizure type or AED was associated with AMH.

This finding is consistent with the small body of pertinent existing literature. It is known menopausal onset ensues when ovarian reserve is depleted; AMH decline is a crude predictor of the onset of menopause, with low levels potentially indicating an age at menopause earlier than age 50 years (Visser et al., 2006). Therefore, the study findings provide support for the report which used historical information that WWE with rare seizures across their lifetime (<20) had a mean age at menopause of 50 years, which is the expected age in developed countries, while WWE with frequent seizures across their lifetime (approximately more than one seizure per month) had a mean age at menopause of 45 years (Harden et al., 2003).

The association between AMH and seizures also fits into the structural hypothesis by which epilepsy and seizures may produce hypothalamic dysregulation. Since the hypothalamus regulates homeostasis for all physiologic and reproductive functions, it has reciprocal connections with most major cortical and sub-cortical structures. The specific pathway connecting structures frequently involved in epileptic networks, the anterior temporal limbic structures (Vismer et al., 2015), directly project to gonadotropin-releasing hormone (GnRH) -producing nuclei in the pre-optic area, which are likely involved in the complex regulation of GnRH production involving the arcuate, periventricular and preoptic nuclei of

the hypothalamus (Pompolo et al., 2005). This dysregulation could result in wasting of the available ovarian follicular pool.

Low AMH concentrations have been reported in another chronic disease, systemic lupus erythematosus (SLE) (Gasparin et al., 2015). This has been described as occurring independently of SLE treatment, although the cytotoxic treatments for SLE do cause ovarian injury and lower AMH concentrations. Women with other chronic rheumatologic diseases including Behcet's, spondyloarthritis and rheumatoid arthritis who had never undergone cytotoxic treatments had AMH concentrations that were markedly lower than controls (Henes et al., 2015). The mechanism of premature ovarian failure in these chronic autoimmune diseases is likely an inflammatory oophoritis (Hoek et al., 1997). This mechanism is not supported by our data as applicable to otherwise healthy WWE.

The second, potentially more provocative finding is that the Sz- group had nearly 50% higher AMH concentrations on average compared to the Sz+ group from both the historical data and prospective data obtained within the study. Further, the possibility of a neuroactive role of AMH is raised by the finding that Sz- group also had approximately 25% higher AMH concentrations on average than the HCs. This should be interpreted with the caveat that AMH values are highly varied across individuals and no subject in this study could be considered to have an abnormal AMH concentration (Visser et al., 2006). AMH was higher in the Sz- group than the Sz+ group in both the historical and the prospective epochs of the study. While this is consistent with AMH signifying endocrine disruption, the finding that AMH was higher in Sz- women than the HCs introduces the possibility as to whether AMH itself, a neuroactive peptide protein, plays a neurophysiologic role in reducing seizure occurrence. The questions raised include those of directionality: does AMH increase in response to an epileptic substrate or does a higher AMH in the setting of a robust ovarian reserve suppress seizures?

With this question in mind, it is clear that AMH is clearly neuroactive. AMH is a member of the TGF-Beta family, and is secreted as a 140 kDa homodimeric precursor. The 25 kDa COOH terminal dimer becomes bioactive following proteolytic cleavage and is active at the AMHR2 receptor. The remaining cleaved portion is involved in AMH synthesis and extracellular transport. AMH is the only known ligand for the AMHR2 receptor, which is widely present in brain areas including the hippocampus, the hypothalamus and other cortical areas (Cimino et al., 2015; Lebeurrier et al., 2008). AMH is a powerful activator of GnRH neurons in vivo and in vitro mouse models, and through this activity increases GnRH response to LH pulsatility (Cimino et al., 2015). Its neurophysiologic activity persisted in the presence of ionotropic amino acid transmission blocking agents applied to brain slice preparations, indicating that this action is independent of NMDA or other AMPA receptors (Cimino et al., 2015).

In fact, AMH is potentially neuroprotective against NMDA-mediated excitotoxicity; its co-injection with NMDA into the intrastriatal region of whole mice resulted in a 35% reduction of lesion volume, and a 65% reduction in NMDA-mediated neuronal cell death when co-applied to primary cell cultures (Lebeurrier et al., 2008). Implications of this aspect of AMH activity could be important for epilepsy given that NMDA-mediated neuronal injury occurs

in animal models (Brandt et al., 2003). The first report of the neuroprotective potential of AMH was in motor neurons wherein the investigators found that AMH promoted the survival and differentiation of embryonic motor neurons in vitro (Wang et al., 2005). AMH also induces the expression of the neuroserpin, which is a potent endogenous neuroprotective factor best described in stroke models (Lebeurrier et al., 2008).

The neuroprotective effect of AMH in the brain can also be examined at a molecular level, wherein its potential to alter seizure activity is most provocative, through a mechanism that involves an altered blood brain barrier (BBB). As a member of the TGF-beta family, AMH influences cellular responses by inducing its membrane proteins to interact with SMAD proteins to form transcriptional complexes that control target genes. (Massague et al., 2005). (The name SMAD derives from its structure as a homolog of both the *Drosophila* protein, mothers against decapentaplegic (MAD) and the *Caenorhabditis elegans* protein SMA (from gene *sma* for small body size)). Breach of the BBB both activates SMAD proteins and is epileptogenic. This breach activates astrocytes, causes inflammation and interferes with buffering for K⁺ and glutamate, the last of which is the most epileptogenic consequence. Blockage of TGF-beta transcription of SMAD proteins can prevent epileptogenesis in the setting of a breached BBB (Cacheaux et al., 2009; David et al., 2009). BBB compromise is increasingly understood as an etiologic contributor to epilepsy as well as consequence of seizures themselves (Marchi et al., 2011). Therefore, endogenous modulation of the cellular response to a BBB breach could affect the course and severity of epilepsy, and AMH is clearly a candidate protein for influencing cellular defense mechanisms.

The clinical effects of AMH have recently been linked to other neurologic diseases. A rapid versus a more moderate decline in AMH in women with multiple sclerosis who were followed for up to 10 years was associated with decreased cortical volume, and risk of disease progression and disability in a large longitudinal study (Graves et al., 2016). AMH is present at very high levels in normal preadolescent boys and declines markedly at puberty; a lower than expected AMH level was associated with a greater number of autistic traits across a cohort of autistic boys (Pankhurst and McLennan, 2012), and its role in the male sex predominance of autism overall may be important.

Shortcomings of this study are that the WEPOD study enrolled a fairly narrow spectrum of women, and enzyme-inducing AEDs and complex polytherapies are underrepresented in this cohort.

5. Conclusions

The findings are hypothesis-generating and these associations should be explored in a larger study using a more diverse epilepsy population and in the laboratory. For example, further clinical studies should include a continuous spectrum of seizure frequency and an in-depth evaluation of seizure type. Emerging evidence regarding the neuroactivity of AMH indicates that it may be important in epilepsy, therefore the effect of AMH on epilepsy animal models merits investigation. Future studies should investigate the association of AMH with seizure occurrence and the direction of this association, as well as its implications as a biomarker for ovarian reserve in women with epilepsy.

Acknowledgements

This study was supported by grants from the Milken Family Foundation and Epilepsy Foundation. We would also like to thank these foundations for their administrative and encouragement throughout the study. The AMH assays were supported by a supplemental grant from the Harvard Catalyst/The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05) and financial contributions from Harvard University and its affiliated academic health care centers.

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Fig. 1.

Correlation between Age and square root AMH.

WWE without seizure, Pearson's correlation -0.453 , $p = 0.003$.

WWE with seizures, Pearson's correlation 0.074 , $p = 0.699$.

Healthy Controls, Pearson's correlation -0.374 , $p = 0.000$.

Table 1

Demographic and epilepsy characteristics of study subjects.

	WWE without seizure n = 40(%)	WWE with seizure n = 30(%)	Healthy Controls n = 97(%)
Age (years)			
Mean ($\pm$ SD)	32.0 ($\pm$ 3.5)	31.4 ($\pm$ 3.4)	31.1 ($\pm$ 4.3)
Median (Range)	32 (26–40)	32 (24–37)	31 (23–40)
Ethnicity			
Hispanic or Latino	3 (7.5)	6 (20)	13 (13.4)
Not Hispanic or Latino	37 (92.5)	24 (80)	84 (86.6)
Race			
Asian	3 (7.5)	1 (3.3)	18 (18.6)
African American/Black	0 (0)	1 (3.3)	16 (16.5)
Native Hawaiian or Pacific Islander	0 (0)	1 (3.3)	1 (1)
White	35 (87.5)	26 (86.7)	54 (55.7)
Other/Mixed	2 (5.0)	1 (3.3)	8 (8.2)
AMH concentration (pg/mL)			
Mean ($\pm$ SD)	3982.00 ($\pm$ 2451)	2776.80 ($\pm$ 2308)	3241.13 ($\pm$ 2647)
Median (Range)	3025 (590–9600)	2165 (24–9876)	2430 (140–15500)
First Quartile Q1	2220	1013	1170
Third Quartile Q3	6058	3603	4570
AED Monotherapy			
LTG	21 (52.5)	11 (36.7)	
LVT	10 (25.0)	7 (23.3)	
Strong enzyme-inducing AED	6 (15.0)	3 (10.0)	
Other	1 (2.5)	2 (6.7)	
AED Polytherapy			
Strong Enzyme-Inducing AED ^a	0 (0)	5 (16.7)	
Other	1 (2.5)	2 (6.7)	
No AED	1 (2.5)	0 (0)	
Seizure Type			
Generalized Only	12 (30)	11 (36.7)	

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	WWE without seizure n = 40(%)	WWE with seizure n = 30(%)	Healthy Controls n = 97(%)
Focal Only	24 (60)	18 (60)	
Generalized and Focal	1 (2.5)	0 (0)	
Unspecified	3 (7.5)	1 (3.3)	
With GTC	31 (77.5)	22 (73.3)	
Without GTC	9 (22.5)	8 (26.7)	