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Does the age of seizure onset relate to menarche and does it matter?

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ABSTRACT

Purpose: To determine whether there is a relationship between the age of seizure onset and the age of menarche. *Methods:* 1144 women with epilepsy (WWE) in the community, ages 18–47 years, provided web-based survey data. We compared the frequencies of the individual differences between their ages of seizure onset and menarche to each other and chance. We determined whether the age of menarche is a predictor of the age of seizure onset and the percentage of the variance that menarche explains. We used two-step cluster analysis to auto-identify a cluster of years relative to the age of menarche that showed the greatest predilection for seizure onset. *Results:* Average age of menarche was 12.55 [95% CI: 12.45–12.65]. It was greater in WWE who developed seizures before versus after menarche (12.70 [12.54–12.86] v 12.42 [12.30–12.54], $p = 0.006$). More WWE had seizure onset during the year of menarche than during any other year (8.3% v expected 2.1%; $p < 0.0001$). Menarche, however, explained only 1% of the variance. Seizure onset frequencies were greatest for an auto-identified cluster that spanned 2 years before to 6 years after menarche and subsumed 49.3% of seizure onset. *Conclusion:* Although the results indicate a significant relationship between the age of seizure onset and the age of menarche, the broader auto-identified perimenarchal cluster that subsumes 49.3% of seizure onset suggests that research target the potential role of the great increase in adrenarchal, as well as gonadarchal, neuroactive steroids that modulate neuronal excitability and seizures during that span.

1. Introduction

Whether the age of seizure onset in women with epilepsy (WWE) relates to the age of menarche has been a longstanding focus of controversy [1–3]. Menarche serves as a readily identifiable point in time marker for the longer process of reproductive maturation (puberty) [1–3]. Puberty includes the genetically programmed but environmentally modifiable courses of adrenarche and gonadarche [4]. Given the potent neuroactive properties of some of the adrenal and gonadal steroids that come online and surge in production during the process of reproductive maturation [4,5], the process may have potential importance for epilepsy. The demonstration of a relationship might identify important modifiable neuroendocrine factors that could be pertinent to the development of epilepsy or the treatment of intractable seizures during this phase of life [6]. It might also contribute to our understanding of the reason why certain forms of epilepsy tend to remit or change in character during this developmental phase of life [7]. The purpose of this study was to determine whether 1) the age of menarche differs between women with epilepsy (WWE) and women in the general population (WGP), 2) the age of menarche differs between WWE who had seizure onset before the age of menarche as compared to WWE who had seizure onset after the age of menarche, 3) the age of seizure onset relates temporally to the age of menarche and 4) the age of seizure onset relates temporally to the broader course of reproductive maturation.

2. Methods

2.1. Subjects and methods

These retrospective data came from the Epilepsy Birth Control Registry (EBCR) web-based survey of 1144 WWE in the community, ages 18–47 years, who provided demographic, epilepsy, antiepileptic drug (AED), reproductive and contraceptive data [8]. We conducted the EBCR survey, located at epilepsybirthcontrolregistry.com, between 2010–2014. The Western Institutional Review Board approved the study. All subjects provided online consent prior to gaining access to the survey. Referral sources included epilepsy organization websites, social

Abbreviations: 95% CI, 95% confidence interval; AED, antiepileptic drug; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; EBCR, Epilepsy Birth Control Registry; $GABA_AR$, γ-aminobutyric acid type A receptor; GnRH, gonadotropin releasing hormone; NMDA, N-methyl-D-aspartate; WGP, women in the general population; WWE, women with epilepsy

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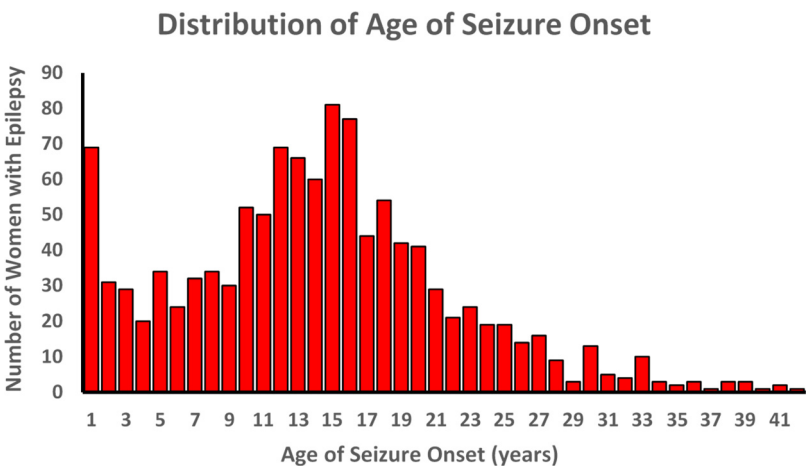

Fig. 1. The number of women with epilepsy who had seizure onset at various ages shows increasing frequencies during the years of late childhood and early-mid adolescence with a peak frequency of 81/1,144 (7.1%) at 15 years of age.

media, internet searches and study brochures posted in clinics. Demographic, seizure and AED characteristics of the study population have been published previously [8].

2.2. Outcomes and statistical analysis

We report the mean ages with 95% confidence intervals (95% CIs), median, range and frequency distributions of the ages of menarche and seizure onset in WWE. We compared the mean age of menarche in WWE to published general population data that correspond best to the years of the EBCR study using the 95% CIs. We compared the mean age of menarche between WWE who had seizure onset before menarche versus WWE who had seizure onset after the age of menarche using the 95% CIs and *t*-test for independent samples. We assessed the relationship between the age of seizure onset and age of menarche by 1) comparing the differences between the two using goodness of fit testing of the observed versus expected frequencies and determination of relative risk (risk ratio) for the observed relative to the expected frequencies, and 2) general linear model univariate ANOVA assessment of the age of menarche as a predictor of the age of seizure onset and the percentage of the variance in the age of seizure onset from the fitted regression line that menarche explains (R^2 value). We explored the existence of a grouping of perimenarchal years that might be associated with a greater frequency of seizure onset using two-step cluster analysis of the frequencies of the individual differences between the age of seizure onset and the age of menarche. This statistical method (SPSS v24) organized data into representative groups based upon similarity of frequencies with each member of the cluster having more in common with other members of the same cluster than with members of the other clusters. The two-step method auto-identifies the number of clusters rather than having it specified by the investigator.

3. Results

3.1. Demographic and seizure characteristics of the study population

The average age of the 1144 participants in the survey was 28.5 years with a standard deviation of 6.9 years and a range of 18–47 years of age. Detailed demographic, seizure and AED characteristics of the study population at the time of the survey have been published previously [8]. 87.4% of the participants resided in the USA. Compared to the general population of the USA as a point of reference, the EBCR participants that responded to the web-based survey in the USA were disproportionately younger and better educated but with lower household income and lower minority representation [8]. The majority of all participants, 59.5%, of the WWE reported having generalized convulsive seizures during the year before the survey whereas 40.8% reported complex partial and 28.4%, simple partial seizures. Complex partial seizures were the most severe seizure type in 20.3% and simple partial, in 20.0%. Only 7.7% of WWE were seizure free. Seizures occurred less than annually in 39.1% of WWE and less than monthly in 51.7%. The survey did not capture the type of AEDs used by women who were already having seizures specifically at or before the age of menarche.

3.2. Average age of menarche and seizure onset

The average age of menarche in the EBCR survey was 12.55 years (95% CI: 12.45–12.65) with median age of 13 and range of 8–20. The mean was similar to that of WGP during the years 1988–1994 which are most pertinent to the EBCR study, 12.53 (12.43–12.63). The mean age was significantly but not substantially greater in WWE who had their age of seizure onset before (N = 509, 44.5%) as compared to after (N = 635, 55.5%) menarche (12.70 [12.54–12.86] v 12.42 [12.30–12.54], *t*-test p = 0.006). The ranges were very similar 8–20 versus 8–19 years respectively.

3.3. Relationship between age of seizure onset and menarche

The average age of seizure onset in WWE was 14.13 years (95% CI: 13.69–14.61) with median age of 15 (7.1%) and range 0–42 (Fig. 1).

More WWE had seizure onset during the year of menarche than during any other year, significantly more than expected by chance (observed 95/1144, 8.3% v expected 24/1144, 2.1%; $\chi^2 = 44.685$, df = 1, $p < 0.0001$), constituting a risk ratio (RR) of 3.96 (95% CI: 2.55–6.15) (Fig. 2). Univariate ANOVA found the age of menarche to be a significant predictor of the age of seizure onset, F (1,12) = 1.933, p = 0.027. The R^2 value of the model, however, explained only 1% of the variance.

3.4. Relationship between age of seizure onset and perimenarchal cluster

The prespecified exploratory two-step cluster analysis of the frequency distribution of the differences between the age of seizure onset and the age of menarche auto-identified 3 clusters. The model summary cluster quality indicated good silhouette measure of cohesion and separation. The cluster with the highest frequencies of WWE for seizure onset consisted of 9 continuous years spanning the 2 years preceding and the 6 years following menarche (Fig. 3). The frequencies of all individual members of this perimenarchal cluster (centroid [62.7],

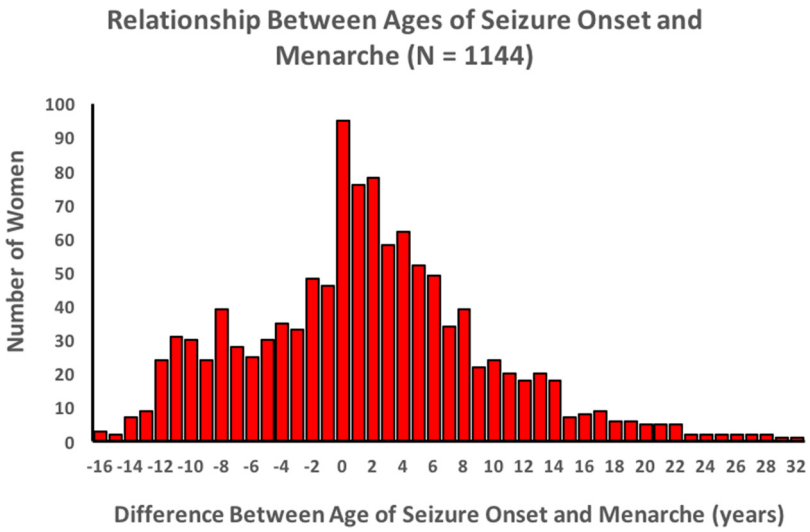

Fig. 2. The analysis of the relationship between the age of seizure onset and the age of menarche finds that more women with epilepsy had their age of seizure onset during the year of menarche than at any other year in relation to menarche and significantly more so than expected (95/1144, 8.3% v 24/1144, 2.1%, $p < 0.0001$). ANOVA analysis, however, finds that the model (R^2 value) explains only 1% of the variance.

range [46–95]) fell outside of the centroids ± two standard deviations (SD) of the second (centroid [27.4], SD [6.8]) and third (centroid [3.9], SD [2.9]) clusters (Fig. 3). This cluster of 9 years accounted for seizure onset in 564/1144, 49.3% of the WWE as compared to an expected value of 216/1144, 18.9% ($\chi^2 = 235.569$, df = 1, $p < 0.0001$). Relative to chance occurrence, the risk ratio (RR) for seizure onset during this cluster (RR = 2.61 [95% CI: 2.28–2.98]) was substantially and significantly greater than for the second (RR = 1.14 [1.03–1.26]) and third clusters (RR = 0.18 [0.14–0.22]).

4. Discussion

4.1. Age of menarche in women with epilepsy

Although the EBCR survey did not have access to the structural brain imaging data of the participants, it is noteworthy that the temporolimbic system, which is so commonly involved in the pathogenesis of epilepsy, may have an important modulatory role among the complex genetic and environmental determinants of the age of menarche [4,9–11]. Animal studies in rats and monkeys have shown that amygdaloid lesions can hasten or delay puberty depending on the precise timing and location of the lesions [9–11]. In this EBCR study, the average age of menarche in WWE (mean ± standard deviation: 12.55 ± 1.69 years) was similar to the age found by Dworetzky et al. [12] (12.4 ± 1.4), Klein et al. [2] (12.2 ± 1.6) and Diamantopoulos and Crumrine [[19]] (12.6 years with range of 10–16). It did not differ from WGP (12.54 (12.44–12.64) during years pertinent to the time of the EBCR study [13]. Svalheim et al. [3] reported a somewhat higher age of menarche (13.1 ± 1.5) which likewise did not differ from their general population controls (13.0 ± 1.46) [3]. We did find that the average age of menarche was significantly, albeit not substantially, greater in WWE who had seizure onset before menarche as compared to WWE with seizure onset after menarche (12.70 [12.54–12.86] versus 12.42 [12.30–12.54], *t*-test p = 0.006). This is consistent with the finding of Klein et al. [2] who also found later onset of menarche in WWE who had seizures before menarche (12.4 ± 1.6 versus 11.7 ± 1.4; p = 0.04). Although the use of AEDs may be a factor, there are reasons to consider a role for epilepsy itself. AED use would not explain the animal data [9–11] or the observation by Hippocrates that menarche is delayed in all forms of epilepsy that date back to infancy [14]. It is noteworthy that both primary generalized [15] and focal onset [16] epilepsy can alter gonadotropin releasing hormone (GnRH)

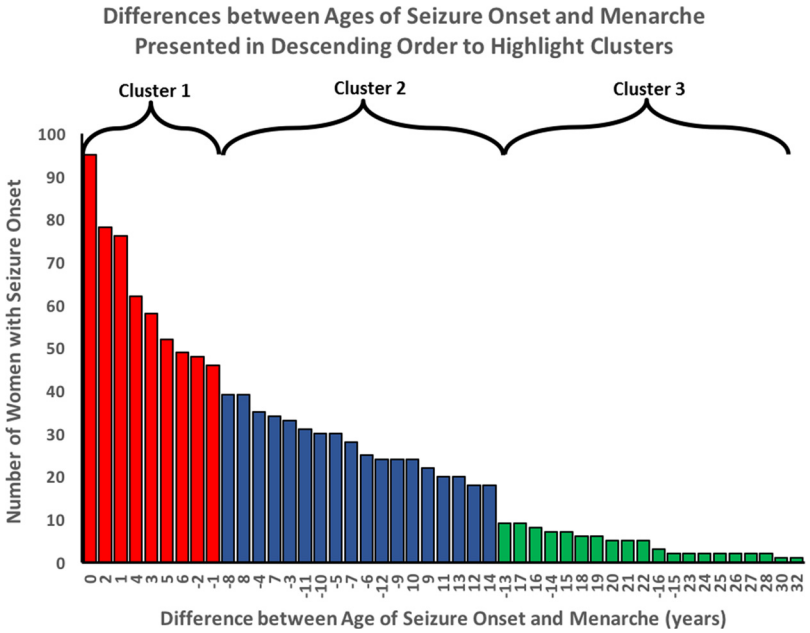

Fig. 3. More women with epilepsy had seizure onset during the year of menarche than during any other year in relation to menarche and more than expected (95/1144, 8.3% v 24/1144, 2.1%, $p < 0.0001$), Two step cluster analysis showed 3 clusters (brackets) with centroids at frequencies of 62.7, 27.4 and 3.9. The cluster with the greatest frequencies, spanning 2 years before through 6 years after menarche, had a greater than expected number of women for age of seizure onset (564/1144, 49.3% v 216/1144, 18.9%, $p < 0.0001$).

pulsatility. In focal onset epilepsy, moreover, there is a lateralized asymmetry in this modulation such that the directional change in pulse frequency relates to the laterality of the epileptic focus [16–18]. Since the development of normal GnRH pulsatility is a prerequisite for the establishment of menarche and ovulatory cycles, it is then possible that epilepsy may alter these processes. Note that epilepsy may also affect another major reproductive milestone, the age of menopause [19]. There is evidence to suggest that WWE may have earlier menopause than WGP such that the greater the number of lifetime seizures, the earlier the age of menopause [19].

4.2. Relationship between age of seizure onset and menarche

This EBCR study finds no overlap between the 95% CIs for seizure onset (13.69–14.61) and menarche (12.45–12.65) yet finds that seizures are more likely to have onset during the year of menarche than during any other year. This greater than expected occurrence of seizure onset during the year of menarche is consistent with the finding of Klein et al. [2] who, in their retrospective study of 94 female adolescents, found that seizure onset occurred during the year of menarche in 17% versus 5.5% expected ($p \leq 0.001$), and during ± 2 years of menarche in 38% versus 22% expected ($p \leq 0.001$). The lack of overlap in 95% CIs, however, can also be consistent with the Svalheim et al. [3] report that a higher frequency of seizure onset occurred between 10–18 compared to 0–9 years of age ($p < 0.01$), similar to the finding of Hauser et al. [20] but found no significant difference in the onset of seizures in the year of menarche compared to the 5 years before or after nor a significant difference in the onset of seizures in the perimenarchal period (menarche ± 2 years) compared to the 5 year periods before and after perimenarche. There are possible explanations for the apparent discordance among the Klein et al. [2] and Svalheim et al. [3] conclusions of these investigations. First, our univariate ANOVA analysis found that the menarche model explained only 1% of the variance of the relationship between seizure onset and menarche. This low percentage suggests that additional factors may warrant consideration to improve the precision of the prediction. Another reason may be that the Klein et al. [2] study made comparisons with expected values whereas Svalheim et al. [3] comparisons were with 5 year epochs before and after the targeted period. A further and perhaps critical reason for discordance, as Klein et al. [2] also point out, may be the selection of comparator years. Whereas the selection of the year of menarche as the target for comparison has an objective basis, the selection of comparator years is subjective. We too found that the frequency of seizure onset increases during late childhood and early-mid adolescence (Fig. 1) but selected a perimenarchal cohort as target for comparison on the basis of a statistically based, auto-identified cluster and compared the frequency of seizure onset during this cluster against both the expected value for the cluster, as well as the values for the other auto-identified clusters with both analyses indicating a greater risk for seizure onset during both the year of menarche and the perimenarchal cluster that spans from 2 years before to 6 years after the year of menarche. Although the relative risk for seizure onset was greater for the age of menarche than for the entire perimenarchal cluster, recognition of the perimenarchal cluster is important because it subsumes 49.3%, rather than just 8.3%, of seizure onset.

4.3. Clinical implications of the relationship of seizure onset to menarche and the perimenarchal cluster

Perhaps the most important reason for consideration of the relationship is its implications for a practical neuroendocrine intervention to prevent the development of epilepsy or to treat intractable seizures during this developmental phase of life. Consideration of the specific types of epilepsy may be critical [1,2,12,21]. In the Klein et al. [2] study, only women who had focal-onset seizures, not primary generalized epilepsy, experienced exacerbation of seizures perimenarchally, consistent with Roscisewska's earlier finding [21]. Specific primary generalized epilepsies, however, may differ. Take, for example, two types which have female preponderance [22]. Juvenile myoclonic epilepsy tends to develop during late childhood or adolescence [6], whereas typical childhood absence seizures tend to abate at this time [7].

With regard to possible biological underpinnings, the auto-identified perimenarchal cluster approximates the span of the adrenarchal process [4]. The adrenarchal process markedly increases production of neuroactive steroids that can affect neuronal excitability and seizures [23–30]. For example, dehydroepiandrosterone sulfate (DHEAS), a potent negative allosteric modulator of the γ-aminobutyric acid type A receptor ($GABA_AR$), increases from about 5–30 to 2–300 mcg/dl between 8–16 years of age to become the most highly concentrated steroid not only in serum but also in cerebrospinal fluid, whether *de novo* brain or plasma derived [27,30,31]. Regional brain concentrations may exceed serum levels [27,30]. Superimposed on the adrenarchal process is the menarchal process which features a massive increase in the production of estradiol and progesterone. Estradiol has complex regionally specific actions [32,33] but is generally considered to be proconvulsant and a promoter of kindling [34,35]. Animal models suggest that estradiol acts via long latency mechanisms to increase dendritic spine and synapse density with a parallel increase in excitatory N-methyl-D-aspartate (NMDA) binding sites, for example, on the lateral branches of the apical dendrites of CA1 hippocampal neurons [36,37]. Estradiol also acts via short latency mechanisms at specific sites to increase excitatory postsynaptic currents [34,37,38] and suppress presynaptic inhibition [39]. Progesterone, in contrast, has a reduced metabolite allopregnanolone which is a potent positive allosteric modulator of the $GABA_A$ receptor [40–42].

Although neurosteroids have complex regionally specific and dose dependent actions [27,30,43], the temporal relationship between the perimenarchal cluster and the age of seizure onset raises the possibility that the massive increase in steroids that are potent negative allosteric modulators of the $GABA_AR$ and positive modulators of NMDA function [28,29], might be a factor in the increased frequency of seizure onset found in this study and by Klein et al. [2] during this phase of development, as well as the exacerbation of focal-onset seizures [2,21] during this time. Might there be a role for the treatment of at-risk individuals with enzyme inducing AEDs which markedly reduce DHEAS levels [44] or with more targeted selective inhibitors of 17–20 lyase (e.g. low-dose ketoconazole) to partially block the conversion of 17-hydroxypregnenolone to DHEA [45,46] or to develop specific inhibitors of DHEA sulfotransferase which block conversion of DHEA to DHEAS without inhibiting sulfatase or cortisol production [47]? Further, since tonic GABAergic inhibition of the thalamocortical circuitry may be a critical factor for the occurrence of typical childhood absence seizures [48,49], might the massive increase in negative allosteric $GABA_AR$ modulatory steroids play a role in the abatement of typical absence seizures during late childhood and adolescence, yet, at the same time, potentiate the conversion of absence to generalized convulsive seizures in perhaps 40% [7]? Finally, since approximately half of the early postmenarchal cycles are anovulatoryand, therefore, estrogen predominant, would girls at increased risk of developing epilepsy, e.g. history of significant head trauma, encephalitis or cerebral malformations, benefit from being cycled with natural progesterone supplement during early postmenarchal cycles [50]?

4.4. Limitations

By way of limitations, this study was retrospective and the surveyed population was limited to WWE between 18–47 years of age who self-selected to participate in an online survey. The WWE were proportionally younger, better educated and had lower family income than the general population [8]. Minorities were underrepresented [8]. The study ascertained types of seizures, not types of epilepsy. It likely

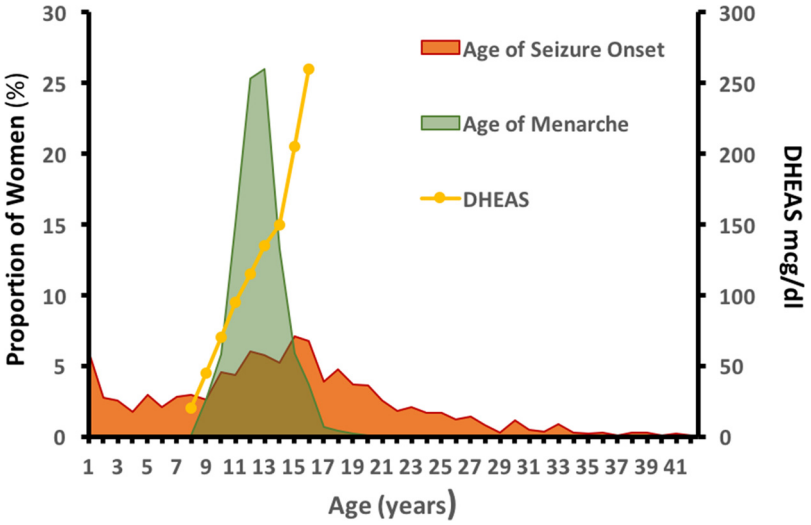

Fig. 4. The auto-identified cluster of perimenarchal years with the greatest frequencies of seizure onset in this study, between 2 years before through 6 years after the age of menarche, approximates the general span of the adrenarchal process, a developmental phase during which there is a massive increase in the production of neuroactive steroids (serum DHEAS levels in this example are adapted from Reiter et al. [31]). The excitatory and inhibitory actions of these neuroactive steroids can modulate neuronal excitability and seizure thresholds. Further investigations should determine whether they may affect the age of seizure onset and occurrence and have differential effects in relation to the type of epilepsy, e.g. neuroexcitatory steroids might contribute to the reported exacerbation of focal onset seizures and the abatement of typical absence seizures or the conversion of absence to generalized convulsions during late childhood and adolescence.

excluded WWE who had more severe forms of epilepsy that are associated with cognitive impairments. Data were not documented by medical records. Although recollection may favor a bias for relating past events to notable landmarks such as menarche, that bias would not explain why seizure onset was reported to be greater than expected even 6 years later. Further, a published study of recall bias as it pertains to the age of menarche found that after 30 years, "recalled and original age at menarche were highly correlated ($r = 0.79$, $p < 0.001$) and original mean menarcheal age (12.93 years, 95%CI: 12.81, 13.06) did not differ from recalled mean menarcheal age (12.85 years, 95%CI: 12.69, 13.00; paired t test, p 0.07) [51]".

4.5. Conclusions

Although the results indicate a significant relationship between the age of seizure onset and the age of menarche, the lack of overlap of their 95% CIs and the auto-identification of a perimenarchal cluster that spans 2 years before through 6 years after menarche and accounts for 49.3% of seizure onset in women of reproductive age, suggests a more complex model and target for research (Fig. 4). The cluster implicates the combined, superimposed and potentially augmentative processes of adrenarche and gonadarche which span these years. These phases of development are accompanied by a massive increase in the production of neuroactive steroids that modulate neuronal excitability. Further investigations should determine whether they may differentially affect the age of seizure onset and seizure occurrence in relation to the type of epilepsy, accounting for the reported exacerbation of focal onset seizures and the abatement of typical absence seizures or their conversion to generalized convulsive seizures during late childhood and adolescence.

Conflict of interests

Dr. Herzog was the principal investigator on this research that was supported by grants from the Epilepsy Foundation and Lundbeck. Mses. Mandle and MacEachern received salary support from Lundbeck.

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