



A survey of antiepileptic drug responses identifies drugs with potential efficacy for seizure control in Wolf–Hirschhorn syndrome

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ABSTRACT

Seizures are present in over 90% of infants and children with Wolf–Hirschhorn syndrome (WHS). When present, they significantly affect quality of life. The goal of this study was to use caregiver reports to describe the comparative efficacies of commonly used antiepileptic medications in a large population of individuals with WHS.

A web-based, confidential caregiver survey was developed to capture seizure semiology and a chronologic record of seizure treatments as well as responses to each treatment. Adverse events for each drug were also cataloged. We received 141 complete survey responses (47% response rate) describing the seizures of individuals ranging in age from 4 months to 61 years (90 females; 51 males). Using the Early Childhood Epilepsy Severity Scale (E-Chess), WHS-associated seizures are demonstrably severe regardless of deletion size. The best-performing antiepileptic drugs (AEDs) for controlling seizures in this cohort were broad spectrum drugs clobazam, levetiracetam, and lamotrigine; whereas, the three commonly used carboxamide class drugs: carbamazepine, phenytoin, and oxcarbazepine, were reported to have little effect on, or even exacerbate, seizures. The carboxamide class drugs, along with phenobarbital and topiramate, were also associated with the highest rate of intolerance due to cooccurrence of adverse events. Levetiracetam, clobazam, and clonazepam demonstrated higher tolerability and comparatively less severe adverse events (Wilcoxon rank sum comparison between performance of levetiracetam and carboxamide class drugs gives a $p < 0.0001$ after multiple comparison adjustment).

This is the largest survey to date assessing WHS seizures. This study design is susceptible to possible bias, as the data are largely drawn from caregiver report and investigators had limited access to medical records. Despite this, our data suggest that the genetic etiology of seizures, together with an accurate electroclinical delineation, are important components of drug selection, even in contiguous gene syndromes which may have complex seizure etiologies.

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Abbreviations: WHS, Wolf–Hirschhorn syndrome; AED, antiepileptic drug.

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1. Introduction

Wolf–Hirschhorn syndrome (WHS; Online Mendelian Inheritance in Man (OMIM) #194190) is a rare contiguous gene deletion syndrome affecting the terminal region of chromosome human chromosome 4, petite arm (4p) [1]. Epilepsy is a serious neurologic challenge for over 90% of individuals with WHS, presenting in early childhood and potentially affecting cognitive development [2]. A previous study involving 87 individuals with WHS determined that seizure types most commonly experienced are generalized tonic–clonic, tonic or clonic, and complex partial [3]. Atypical absences with a myoclonic component occur in one-third of children [3]. Approximately 40–50% of individuals with WHS experience status epilepticus with prolonged, life-threatening seizures [1,3].

There are now over 30 FDA-approved drugs for seizure control. Currently, seizure types and electroclinical presentations play significant roles in driving drug selection for epilepsy treatment [4], while genetic etiology is only beginning to be considered a relevant factor [5]. As advances in genetics continue to contribute to the understanding of the underlying molecular etiology of epilepsy, studies demonstrating efficacies of one drug over another based on specific genetic causes become increasingly important [6].

Given the complex seizure semiology of WHS individuals, we aimed to understand whether certain drugs confer better overall seizure control than others. We developed, tested, and implemented a web-based confidential survey which was distributed to approximately 300 families in the 4p- Support Group. The survey was designed to capture caregiver-observed seizure types [7] and presentations, the antiepileptic drugs (AEDs) used to control seizures in the chronological order in which they were taken, and the individuals' responses to these drugs in the form of seizure control and adverse events while on the drug. Here, we present an analysis of the survey results, which indicates that certain drugs currently in use in this population demonstrate significantly better performance metrics in controlling seizures than others, despite the complex seizure presentation of this disorder.

2. Methods

2.1. Cohort

A study cohort was recruited from approximately 300 families who are members of the 4p- Support Group. This group is US-based, but does also include a minority of families from Europe and Asia. Inclusion criteria were the following: 1) the individual must have a diagnosis of WHS; 2) the diagnosis must have been confirmed by clinical cytogenetic or molecular testing consisting of one or more of the following: positive fluorescence in situ hybridization (FISH), positive karyotype, and positive cytogenomic microarray; and 3) the individual must have experienced at least one seizure and have received at least one type of seizure treatment. Exclusion criteria were the following: 1) no seizures were experienced despite having a WHS diagnosis, and 2) lack of molecular testing confirming a WHS diagnosis. In all cases, the survey was completed by a caregiver who was familiar with the affected individual's seizures and responses to treatments. When medical records were available ($N = 22$), they were used to confirm caregiver answers to survey questions. Families also submitted copies of the molecular diagnostic reports when available ($N = 50$).

2.2. Survey design

A survey to capture seizure phenotypes and treatment responses was developed in accordance with previously published survey studies designed for similar purposes for both human chromosome 15, long arm (15q) duplication syndrome and Angelman syndrome (AS) [8,9]. The survey consisted of three parts: 1) a demographics section to collect information including name of WHS-affected individual, age, gender, and genetic testing methods used to confirm diagnosis; 2) a seizure history section to collect information such as age of seizure onset, types of seizures experienced [7], and types seizure triggers; and 3) a seizure treatments and treatment responses section to collect information concerning treatments tried, and responses to each treatment, in chronological order of use (see Supplemental material for a complete list of the survey questions). Reported treatment responses were scored on a 5 point scale: 5 = complete seizure control (as defined by an absence of seizures for 6 months while on the treatment), 4 = 50% or greater reduction in seizure frequency, 3 = less than 50% reduction in seizure frequency, 2 = no change in seizure frequency or a response of "I don't know," and 1 = increase frequency of seizures or treatment had to be discontinued due to intolerable cooccurrence of adverse events.

To improve the utility and accuracy of the survey, a focus group of four parent volunteers whose children met inclusion criteria and a research scientist (LM) were assembled to discuss each question in a private cognitive interview with each parent. The survey was revised in accordance with feedback from the interviews and edited for clarity and brevity (see Supplemental information). The final survey was made available through the Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant platform REDCap (Research Electronic Data Capture; <https://catalyst.harvard.edu/services/redcap/>).

2.3. Seizure severity scoring

Seizure severities were classified using a modified Early Childhood Epilepsy Severity Scale (E-Chess). Scores were calculated following the method of the original E-Chess paper [10] except as described below. In short, scoring was calculated as follows for the four severity indices: time period over which seizures occur (1 point = less than a month, 2 points = 1–6 months, 3 points = more than 6 months); number of seizure types (1 point = one seizure type, 2 points = two seizure types, 3 points = 3 or more seizure types); number of anticonvulsants used (0 points = none, 2 points = one or two anticonvulsants used, 3 points = more than two used); and response to treatment (1 point = complete cessation of seizures, 2 points = partial cessation of seizures, 3 points = no improvement or worsening of seizures). Two indices of the six-point scale were omitted, namely frequency of seizures (weekly, daily, more than daily) and occurrence/duration of status seizures. These components were omitted for the following reasons: seizure frequency varies widely, even within the same individual, and varies depending on age in the WHS group. Since our cohort had a very wide age range, this variable was unlikely to be contributory. Regarding the status seizure component, Humphrey et al. reported that this component was not statistically predictive of severity while the other five indicators were, and dropped the component from further analyses in their statistical modeling of seizure severity [10].

The study, recruitment materials and methods, participant consent forms, and survey questions were approved by the University of Utah Institutional Review Board (IRB #00064655).

2.4. Statistical analyses

Calculations and statistical analyses were performed using Excel for data assembly, scoring, basic calculations (e.g., mean, standard error, median, quartile calculations), and for generating bar graphs, charts, tables, histograms, and box plots. For statistical hypothesis tests, the statistical software package Statistical Analysis Software (SAS) 9.4 was used. Because our data either take discrete values or are highly skewed, we used the Wilcoxon rank sum and Kruskal–Wallis tests to compare outcomes between groups, as indicated in the text. A p value of 0.05 or less was taken to be significant, except in cases of multiple testing, in which case Bonferroni correction was applied to the significance test, as indicated in the text. Drugs were reported as being used as monotherapy or as combinations; however, because of our small sample size ($N = 141$) as compared with the number of drugs ($N = 22$), we performed analyses on each drug as though the drug were not used in combination in order to observe overall efficacy on an individual drug basis.

3. Results

One hundred and forty-three surveys were completed and received from the estimated 300 families in the 4p- Support Group, a nonprofit organization for families of individuals with deletions on 4p which is based in the USA but with worldwide membership. One participant's responses were excluded from analysis, and one participant's responses were modified: 1) an individual, whose genetic analyses were negative by karyotype and FISH, but who nevertheless had received a clinical diagnosis of WHS, was later found to not have a deletion on 4p through

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