Longitudinal Relationship Between Seizure Burden and Developmental Progression and the Implications on Quality of Life in Children with CDKL5 Deficiency Disorder

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BACKGROUND/AIMS

The International CDKL5 Disorder Database (ICCD) collects information from families/caregivers of a child with CDD through completion of an online or paper questionnaire. To date, this worldwide registry has ascertainment from over 40 countries with data from nearly 350 families of individuals with CDD ranging in age from 2 months to 35 years at ascertainment.

Families of 183 individuals with a confirmed pathogenic mutation were administered a follow-up questionnaire from mid 2018 onwards

Aims

1. To investigate the effect of seizure and medication burden at first contact with the ICDD on subsequent development and clinical severity.
2. To compare the Quality of Life (QOL) of those whose development had progressed, stabilised or regressed over two time points taking into account age at first time point and the duration of the interval between the two time points.

AIM 1

EXPOSURE

1. **Seizure burden** defined as high (≥ 5 seizures per day) vs low (<5 seizures per day) at baseline
2. **Medication burden** (as an additional proxy measure of seizure severity) defined high (≥ 3 antiseizure medications per day) and low (<3 antiseizure medication per day) at baseline

OUTCOME

a. CDD Severity Score *(previously published score[1]):*
Series of functional items and comorbidities consolidated to three major domains namely
1) motor (max score: 25), 2) comorbidity (max score: 17) and 3) behaviour, speech and sleep (max score: 15).
Total severity score created by summing up the three domain scores (max score: 57).
b. CDKL5 Developmental Score (previously published score[2])
This is calculated with one point awarded for each of the following: independent sitting, independent standing, independent walking, raking grasp, pincer grasp, babbling and single word. Higher scores indicate attainment of more milestones.

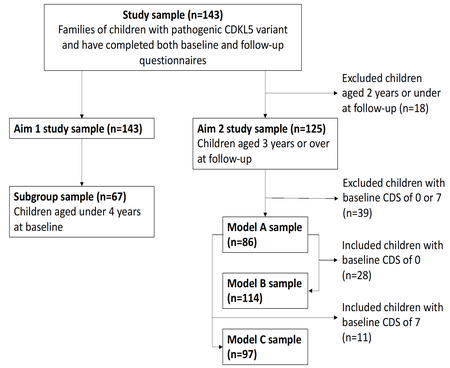
AIM 2

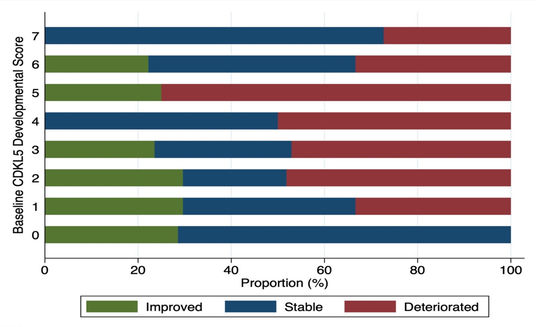
EXPOSURE

CDKL5 Development Score used to describe change in the development of the child with CDD from baseline to follow-up as improved, stable, or deteriorated.

Change in CDKL5 Developmental Score by baseline score aged ≥3 years at follow-up.

Study sample inclusion and exclusion criteria





QI- Disability quality of life score
Created from 32 items rated on a five-point Likert scale,[3] grouped into six domains. Mean of these domains provides a total score.

Statistical analyses – Aim 1

- Follow-up CDD severity score and CDS were assessed by four models based on seizure and medication burden (high vs low) at baseline using multivariable linear regression and negative binomial regression respectively.
- Models were repeated for those individuals whose age at baseline was <4years
- Covariates: Age at baseline, gender, mutation group and follow-up duration.

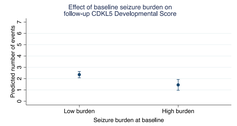
Statistical analyses – Aim 2

- The associations between change in CDS from baseline to follow-up and QOL scores at follow-up (total and domain) were modelled using multivariable linear regression.
- Three models (Model A,B and C) were created to fully accommodate individuals with baseline CDS of 0 and 7.
- Covariates: Age at baseline, gender, mutation group and follow-up duration.

RESULTS

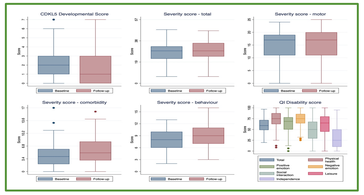
AIM 1

- The expected follow-up *CDKL5 Developmental Scores* for individuals with high seizure burden were marginally lower [b-0.49; 95% CI -0.84, -0.13) than that of those with low seizure burden.

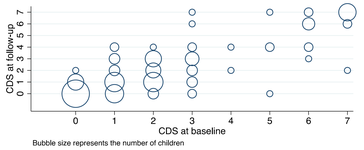


- There was a probable increase in the mean follow-up total severity scores for individuals with high medication burden when compared to those with low medication burden.
- There was some increase in the average gastrointestinal domain scores for those with high medication burden relative to those with low medication burden, particularly so in the under 4 years age group [β 1.27; 95% CI 0.09,2.45].

Baseline and follow-up CDKL5 Developmental Score and CDKL5 Developmental Disorder Severity (total and domain) scores and follow-up QI-Disability (total and domain) scores.



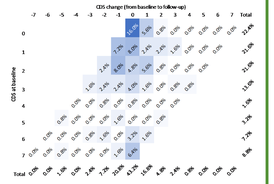
Relationship between CDS at baseline and follow-up in 125 children with CDKL5 Deficiency Disorder aged 3 years or above at follow-up.



Bubble size represents the number of children

AIM 2

- 80.8% and 92.8% of the 125 children included in the analysis achieved at most a 1 or 2 point change in CDS, respectively.



- The average total QI-Disability score was 5.6 (95% CI -0.2,11.5) points higher among those with improved compared with stable or deteriorating CDS and 8.5 (95% CI 3.1,13.8) points lower for those with deteriorating compared to stable or improved CDS.

CONCLUSIONS

- Developmental scores were marginally poorer in those with high seizure burden at first contact compared with those with lower seizure burden.
- In those under four years at baseline gastro-intestinal and feeding difficulties were also more severe in those with high medication burden.
- However, we did not find a relationship between seizure burden at first contact and subsequent total severity.
- There was a strong but not unexpected association between the developmental trajectory and quality of life in that those whose development had improved or was stable had better subsequent quality of life than those whose development had regressed.
- Much more needs to be known about the natural history of CDD and the factors that influence both developmental progress and deterioration
- It is hoped that this study may be a first step towards finding answers to these questions.

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