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CLCN4-related Neurodevelopmental Condition

Fact sheet

What is *CLCN4*-related neurodevelopmental condition (*CLCN4*-NDD)?

CLCN4-NDD is a genetic condition. Variants in the the *CLCN4* gene often cause cognitive impairment, motor (movement) challenges, sleep problems, and epilepsy (1–3) *CLCN4*-NDD is caused by pathogenic or likely pathogenic variants in the *CLCN4* gene, which encodes for the CIC-4 chloride channel which is highly expressed in the brain. The gene is located on the X-chromosome, which has been linked to higher pathology in males with a pathogenic variant (4). However, females with a *de novo CLCN4* variant are also reported to have severe pathology and cognitive impairment, especially compared to females with inherited variants.

Speech and Language

The terms 'speech' and 'language' are often used interchangeably; yet, they are categorised differently by a speech pathologist, with has implications for therapy:

Speech is focused on speech sounds. This includes sound accuracy, articulation, voicing, resonance (e.g., nasality), and prosody (e.g., stress and rhythm).

Language involves the understanding and use of words (vocabulary) and sentences (grammar).

What are the associated health and medical conditions seen in *CLCN4*-NDD?

- **Learning difficulties**: Most people with *CLCN4*-NDD experience mild-to-severe cognitive impairment (1,2).
- **Mental health and behaviour:** Autism spectrum disorder (ASD) is frequently reported in this group, as well as attention difficulties, anxiety, and mood conditions (3,6)
- **Motor (movement) disorder:** Gross and fine motor delays are common in this group. Infantile hypotonia (low tone) is also an important feature, that can often affect the oral-motor structures required for speech and feeding.
- **Epilepsy and seizures:** Epilepsy affects nearly 50% of people with *CLCN4*-NDD. Seizures often present by 3-years-old and can be resistant to standard antiseizure medications (3,7,8)
- **Brain changes:** MRI studies often find changes involving the white matter of the brain. The corpus callosum is often found to be thinner, and occasionally absent in affected people (1,9,10).
- **Gastrointestinal difficulties:** Reflux disorders and chronic constipation are increasingly being recognised in this group, affecting growth milestones especially in *de novo* females. *De novo* females are also reported to experience greater feeding challenges than males or inherited females. Nutritional supplementation via a

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50 Flemington Road, Parkville VIC 3052
geneticsofspeech@mcri.edu.au

gastronomy tube is sometimes required to support adequate nutrition (6).

What are the common speech and language features in children with *CLCN4*-NDD?

Communication difficulties represent the most common feature in this group, affecting 100% of males and 95% of *de novo* females in the largest cohort studied to date (4). Difficulties understanding and expressing language are a consistent challenge across the group. However, the trajectory of speech and language development varies across people. Some children produce their first words within typical development (around 1 year old), while some adults have not yet said their first word (5). In contrast, the progression to two-word phrases and sentences was consistently delayed, which in turn prevented communication development from a need based, to functional social expression. This was identified as an important barrier in this group, who all showed a strong social desire to communicate.

How can speech pathologists/therapists support children with *CLCN4*-NDD?

People with *CLCN4*-NDD require comprehensive and dynamic assessment to inform the most appropriate diagnosis and therapy options. These assessments should include language (expressive and receptive), speech (sound stimulability, intelligibility, speech errors), oral-motor assessment, and social communication. Frequent reassessment is also recommended to monitor progress and ensure speech, language, and social communication goals are relevant and meaningful to the person and their family (11).

There is currently no research on speech and language therapies specific for people with *CLCN4*-NDD. However, evidence-based practice must include a person and family centred approach to assessment and therapies that are tailored to the person's strengths and challenges.

Consistent reports of speech and language delays in *CLCN4*-NDD, especially regarding the transition from first words to 2-4 word phrases, emphasise the benefit of early speech pathology intervention to support language learning and early speech milestones (5). Given the persisting nature of speech challenges, AAC should be implemented early, and regularly reassessed to ensure the system provided is relevant to the child, family, educational and social environment. AAC interventions may involve low-tech approaches (e.g., key word sign, communication books). In some instances, more than one AAC system may be required to support the person's communication across environments and communication settings. Education to families about the benefit of AAC to support overall language development, and provide an opportunity for social connection, is essential. For people with spoken language, motor speech therapy that follows motor learning principles will support speech intelligibility and naturalness.

Assessment/evaluation

Speech assessment should include:

- Speech production skills across single sound, word, and sentence level. This will help specific diagnosis (e.g., phonological disorder, articulation disorder, apraxia of speech).
- Receptive, expressive, and social language skills.
- AAC assessment to determine the best system for your child's needs.
- Literacy assessment.

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- Environmental supports to optimise practical communication needs (e.g., visual schedules, desk position in the classroom etc.).

Further information and support:

- For more information on speech and language research in *CLCN4*-NDD**: here**
- More information on AAC: AAC Fact Sheet

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