Burden of Aromatic L-Amino Acid Decarboxylase (AADC) Deficiency in Italian Patients from Symptomatology and Motor Development Perspective

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1. Background and aims

- Aromatic L-Amino Acid Decarboxylase Deficiency (AADC-d) is a rare genetic disorder caused by mutations in the dopa decarboxylase (DDC) gene that affects production of key neurotransmitters, namely catecholamines and tryptamines.
- The disease manifests with a plethora of motor, cognitive and autonomic signs and symptoms eg: oculogyric crisis, hypotonia, and delay in motor and cognitive development[1,2,3].
- Literature describing the burden of disease in European AADC-d patients is scarce[2].
- The aim of this study was to describe the burden of AADC deficiency in Italy focusing on patient symptoms and developmental motor milestones.

2. Methods

- Discussion guides were developed by international AADC-d specialists and wording adaptation to local language was validated by one Italian expert.
- Five Italian clinicians with experience on treating AADC-d patients were solicited to participate in this study.
- Respondent clinicians (4) completed a questionnaire for each anonymized patient consulting clinical records before participating in individual interviews.
- Data analysis was undertaken by Open Health in line with a pre-agreed statistical analysis plan, using Stata 14 (StataCorp LLC) and Microsoft Excel.

3. Results

- Information was provided for 11 patients cases.
- The mean (range) number of patients cared by the 4 clinicians at time of survey was 2.50 (1-6)
- According to motor milestone achievement, patients were classified in three groups:
  - 7 patients able to walk assisted or unassisted,
  - 2 able to sit unassisted,
  - 2 with no motor function OR with head control only

DEMOGRAPHICS

- Their mean (range) age at last follow up was 21.55 (3-40) years.
- Their mean (range) follow up length was 5.36 (2-8) years (one patient no longer followed up).
- 73% of the 11 patients were male; 82% Caucasian and 18% African in ethnicity.
- The disease genotype was known for all patients (table 1)
  - Patients with the same mutation were found to have different phenotypes (Eg. 1 patient with mutation *c.1543C>T (p.Ser250Phe)* was able to walk whereas 2 other showed no motor function or head control only).

Table 1. Types of DDC gene mutation identified for the 11 patients, with percentages

Type of mutation	Overall (n=11)	
	n	%
c.1543C>T (p.Ser250Phe)	3	27%
c.105delC (p.Tyr37Thrfs*5)/c.710 T>C (p.F237S)	2	18%
p.Arg375 Cys	2	18%
Missense mutation of the DCC gene	2	18%
AADC gene variants: [p.Ala91Val (c.272C> T) and p.Cys410Gly (c.1228T> G)]	1	9%
c.843C>G (p.Cys281Trp)/c.1085T>C (p.Met362Thr)	1	9%

DIAGNOSIS

- Time to diagnosis from first symptoms was longer for a higher proportion of patients achieving a more developed motor milestone.
  - 57% of patients walking unassisted were diagnosed after 19 years, 29% before 2 years and the other 14% between 2 and 6 years from symptoms onset.
  - 100% of patients able to sit unassisted were diagnosed within 2 years
  - 50% of patients with no motor function/head control only (no matter the milestone achieved) were diagnosed between 2 and 6 years from symptom onset and 50% before being 2 years old.

3. Results (continued)

SYMPTOMS

- Among the groups of symptoms characterized in the AADC-d consensus guideline[2], all patients presented movement disorders and gastrointestinal symptoms, while 91% had other central nervous system (CNS) symptoms (Figure 1).

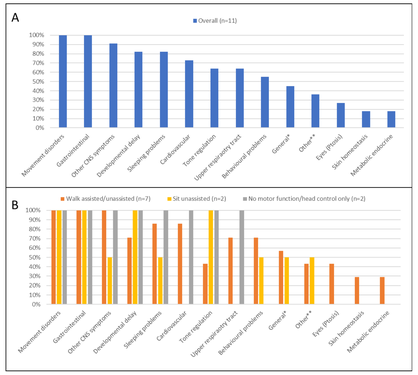

Figure 1. Overview of groups of symptoms reported for the 11 Italian patients (grouped by categories based in Wassenberg et al[2]). A. For the overall sample. B. Dissected per milestone achievement group. *"General" includes: feeding/swallowing problems, failure to thrive, gastrointestinal problems unspecified and depressive disorders. **"Other" includes signs not classifiable within the above categories: Sleep apnea, recurrent respiratory infections, progressive kyphoscoliosis, severe gastroesophageal reflux, severe asthenia, marfanoid habitus, and craniofacial dysmorphism.

- The 10 most recorded individual symptoms (detailed within groups described in Figure 1) for the overall Italian sample were: fatigability (82%), diarrhoea (82%), insomnia (82%), delayed cognitive (82%) and speech development (73%), orthostatic hypotension (73%), dyskinesia (73%), dystonia (64%), delayed motor development (55%) and excessive drooling (55%) (Figure 2).

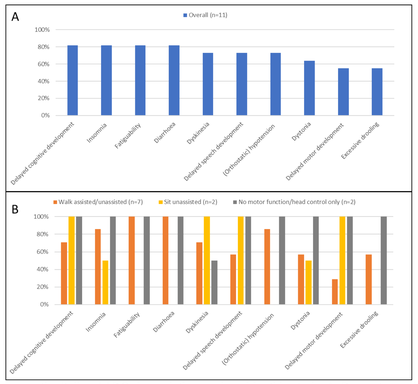

Figure 2. Top 10 symptoms found among the Italian AADC-d population analysed for this study. A. Percentage of overall patients reporting each of these symptoms. B. Percentage of patients reporting these symptoms split by motor milestone achievement group.

3. Results (continued)

- Patients able to walk unassisted had generally a wider range of symptoms (Figure 1), and patients with no motor function/head control experienced them more frequently (Figure 3).

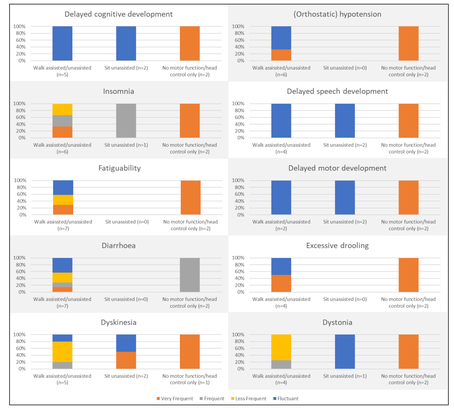

Figure 3. Frequency reported for each of the top 10 symptoms split per motor milestone achievement group. Since responses were provided as free text, the following assumptions were applied during the analysis: Very Frequent= "permanent", "all the time", "constant", "daily", "20/day", "2/day", "permanent with exacerbations", "1/48 hours", "5/week", "every 2 days", "2-3 weekly", "almost permanent", "permanent gentle", "constantly", "very pronounced"; Frequent= "Weekly", "30% of the time", "1/week", "2/month"; Less frequent= "monthly", "1/month", "1-2 monthly", "2-3 yearly", "occasional"; Fluctuant = "NA", "not reported", "sporadic", "fluctuant", "sporadic", other unspecified response, undefined.

- 5 most frequent causes of hospitalization were reported for the Italian cohort of patients with a wider mix reported for patients able to walk or sit unassisted (Table 3).

Table 3. Number (and percentage) of patients who had at least one hospitalisation per type of cause since diagnosis; results are not mutually exclusive as patients may have experienced more than one type of cause of hospitalisation (split for each motor milestone achievement group).

Cause of hospitalisation	Walk unassisted (n=7)		Sit unassisted (n=2)		No motor function/head control only (n=2)	
	n	%	n	%	n	%
Uncontrollable movements	4	57%	0	0%	2	100%
Epileptic seizures	0	0%	1	50%	0	0%
Fever	0	0%	1	50%	0	0%
Hypoglycaemia	1	14%	0	0%	0	0%
Idiopathic nephrotic syndrome	1	14%	0	0%	0	0%

4. CONCLUSIONS

- To our best knowledge this is the first study that describes patient characteristics associated with the burden of AADC deficiency in Italian patients.
- This study unveils the lesser known disease severity of AADC-d patients that retain ambulation (ptosis, kyphoscoliosis, depression, feeding issues, failure to thrive or behavioral problems among others) which represent a good proportion of the Italian AADC-d population.
- These results may inform future health technology assessment submissions.

REFERENCES

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