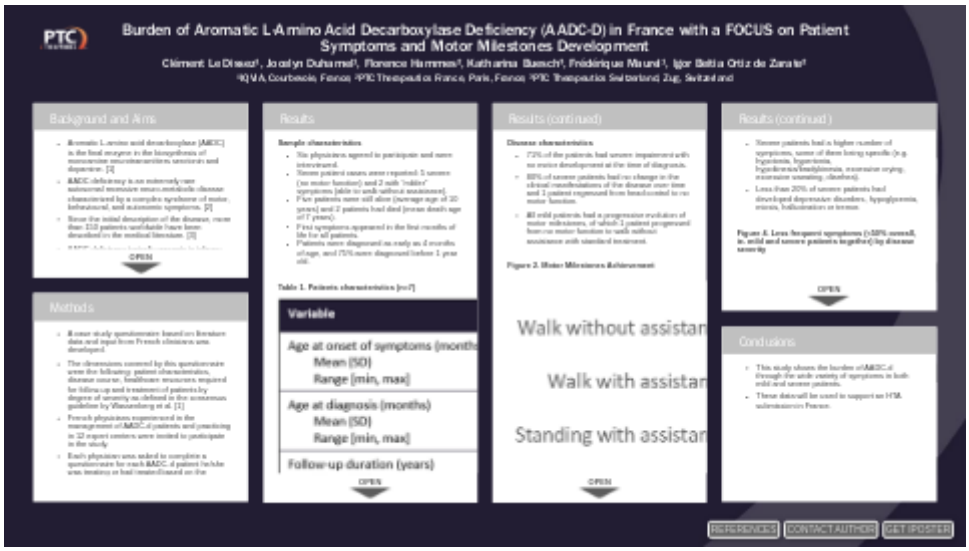
Burden of Aromatic L-Amino Acid Decarboxylase Deficiency (AADC-D) in France with a FOCUS on Patient Symptoms and Motor Milestones Development



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BACKGROUND AND AIMS

- Aromatic L-amino acid decarboxylase (AADC) is the final enzyme in the biosynthesis of monoamine neurotransmitters serotonin and dopamine. [1]
- AADC deficiency is an extremely rare autosomal recessive neuro-metabolic disease characterized by a complex syndrome of motor, behavioural, and autonomic symptoms. [2]
- Since the initial description of the disease, more than 150 patients worldwide have been described in the medical literature. [3]
- AADC deficiency typically presents in infancy with hypotonia, oculogyric crises, and developmental delay. [2]
- While most patients present a severe phenotype (no or very limited developmental milestones, fully dependent), a few patients with a milder course (mild delay in developmental milestones, ambulatory without assistance, mild intellectual disability) are known. [1]
- The aim of this study, part of a global study assessing the burden of AADC-d in Europe, was to describe symptoms and developmental motor milestones in French patients.

METHODS

- A case study questionnaire based on literature data and input from French clinicians was developed.
- The dimensions covered by this questionnaire were the following: patient characteristics, disease course, healthcare resources required for follow-up and treatment of patients by degree of severity as defined in the consensus guideline by Wassenberg et al. [1]
- French physicians experienced in the management of AADC-d patients and practicing in 12 expert centers were invited to participate in the study.
- Each physician was asked to complete a questionnaire for each AADC-d patient he/she was treating or had treated based on the information available in medical records and his/her knowledge of his/her patient(s).

RESULTS

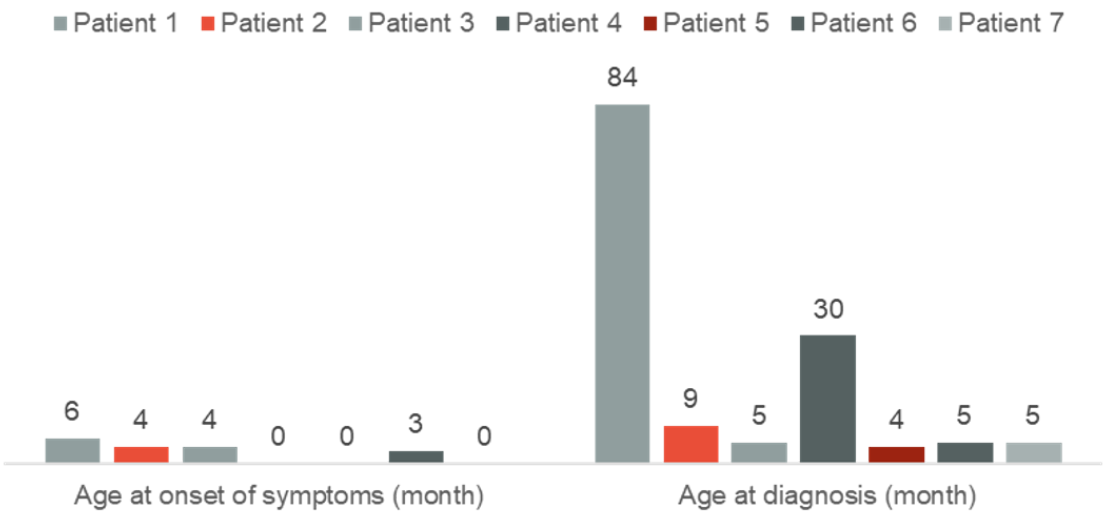
Sample characteristics

- Six physicians agreed to participate and were interviewed.
- Seven patient cases were reported: 5 severe (no motor function) and 2 with “milder” symptoms (able to walk without assistance).
- Five patients were still alive (average age of 10 years) and 2 patients had died (mean death age of 7 years).
- First symptoms appeared in the first months of life for all patients.
- Patients were diagnosed as early as 4 months of age, and 75% were diagnosed before 1 year old.

Table 1. Patients characteristics (n=7)

Variable	N=7
Age at onset of symptoms (months)	
Mean (SD)	2.4 (2.4)
Range [min, max]	[0, 6]
Age at diagnosis (months)	
Mean (SD)	20.3 (29.6)
Range [min, max]	[4, 84]
Follow-up duration (years)	
Mean (SD)	4.2 (3.6)
Age at last follow-up visit, patients alive (years)	
Mean (SD)	10 (5.8)
Age at last follow-up visit, deceased patients (years)	
Mean (SD)	7 (1.4)
Gender, n (%)	
Male	4 (57%)
Female	3 (43%)
Severity, n (%)	
Mild	2 (29%)
Moderate	0
Severe	5 (71%)

Figure 1. Age at symptoms onset & diagnostic

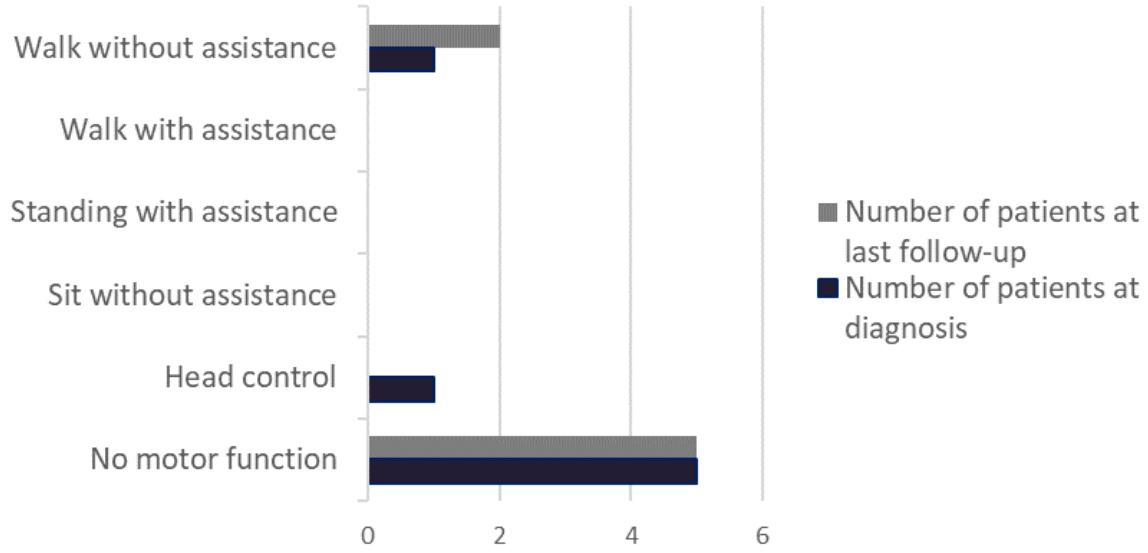

Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
6
4
4
0
0
3
0
84
9
5
30
4
5
5
Age at onset of symptoms (month)
Age at diagnosis (month)

RESULTS (CONTINUED)

Disease characteristics

- 71% of the patients had severe impairment with no motor development at the time of diagnosis.
- 80% of severe patients had no change in the clinical manifestations of the disease over time and 1 patient regressed from head control to no motor function.
- All mild patients had a progressive evolution of motor milestones, of which 1 patient progressed from no motor function to walk without assistance with standard treatment.

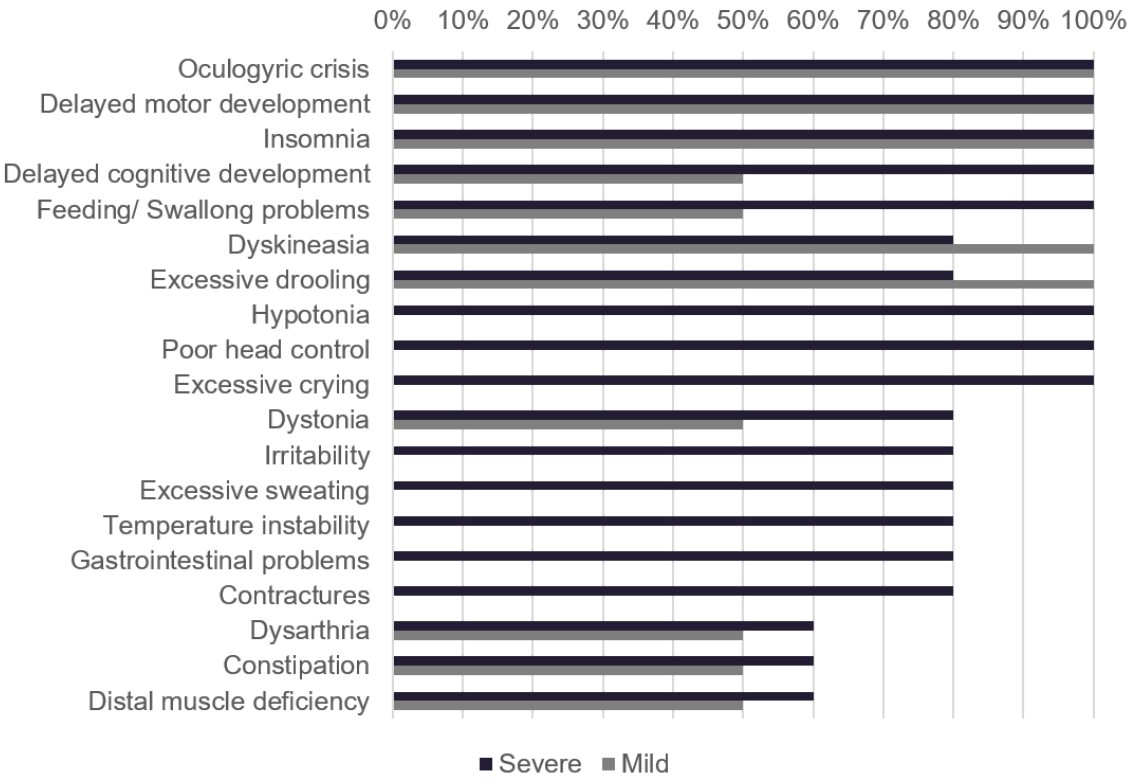
Figure 2. Motor Milestones Achievement



Symptoms

- All patients have developed typical symptoms of AADC-d: oculogyric crisis, delayed motor and speech development and insomnia.
- Over 75% of patients had developed dyskinesia, delayed cognitive development, excessive drooling or feeding problems.

Figure 3. Frequent symptoms (≥50% overall, ie. mild and severe patients together) by disease severity

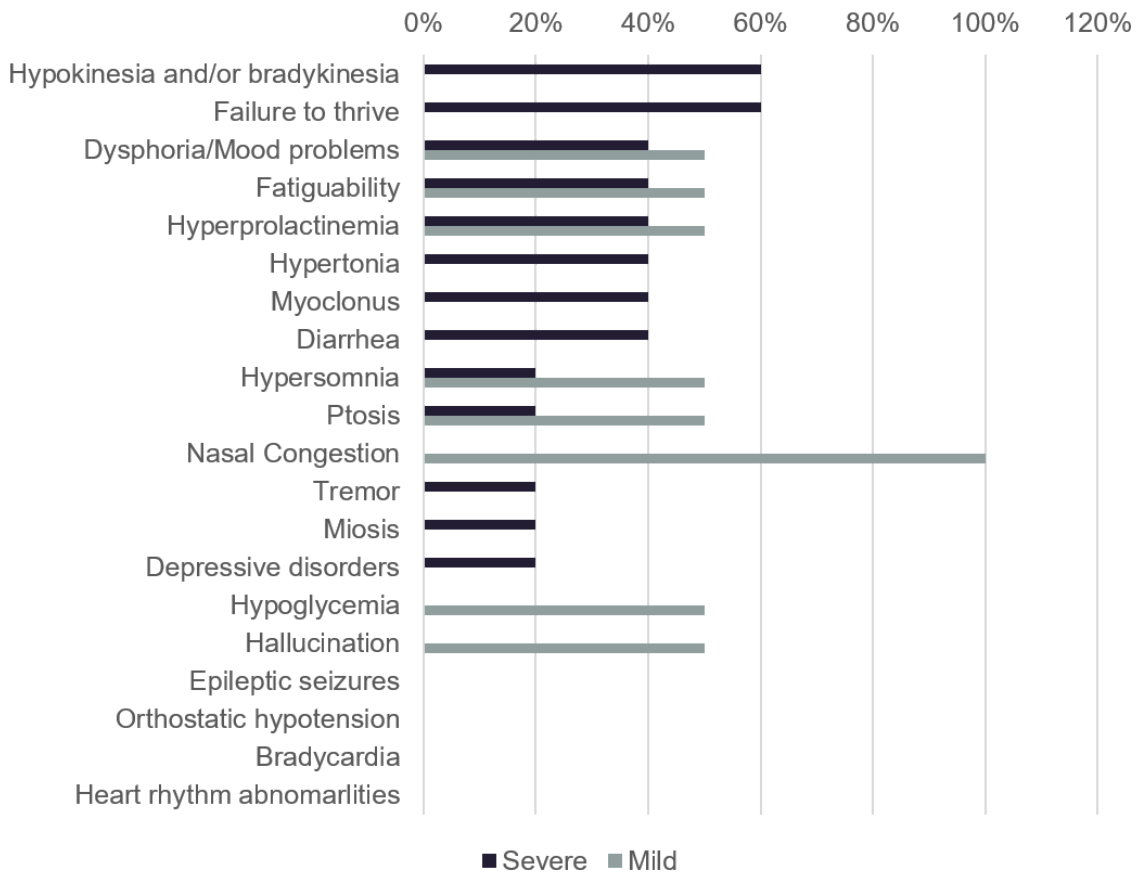

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Oculogyric crisis
Delayed motor development
Insomnia
Delayed cognitive development
Feeding/ Swallong problems
Dyskineasia
Excessive drooling
Hypotonia
Poor head control
Excessive crying
Dystonia
Irritability
Excessive sweating
Temperature instability
Gastrointestinal problems
Contractures
Dysarthria
Constipation
Distal muscle deficiency
Severe
Mild

RESULTS (CONTINUED)

- Severe patients had a higher number of symptoms, some of them being specific (e.g. hypotonia, hypertonia, hypokinesia/bradykinesia, excessive crying, excessive sweating, diarrhea).

- Less than 20% of severe patients had developed depressive disorders, hypoglycemia, miosis, hallucination or tremor.

Figure 4. Less frequent symptoms (<50% overall, ie. mild and severe patients together) by disease severity



CONCLUSIONS

- This study shows the burden of AADC-d through the wide variety of symptoms in both mild and severe patients.
- These data will be used to support an HTA submission in France.

REFERENCES

1. Wassenberg T et al. Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. Orphanet J Rare Dis. 2017;12(1):12
2. Pearson T et al. AADC Deficiency from infancy to adulthood: symptoms and developmental outcome in an international cohort of 63 patients. J Inherit Metab Dis. 2020;43:1121-1130
3. Kuseyri Hübschmann, Opladen T. Aromatic L-amino acid decarboxylase deficiency. Orphanet. July 2020