Consensus Delphi
"AADCd Aromatic L-amino acid decarboxylase deficiency”

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Statement 1. AADC clinical manifestations:

	1	2	3	4	5	TOT
1.1 There is high phenotypic variability, partly related to age at onset.	0	0	7	6	0	13
	0%		100%			100%
1.2 Predominating clinical manifestations at presentation in early-onset forms are autonomic, associated with hypotonia/movement disorder, and developmental delay.	0	0	1	6	6	13
	0%		100%			100%
1.3 There are significant differences in clinical characteristics between early-onset and adult-onset cases.		2	3	5	3	13
	15%		85%			100%
1.4 Regardless of clinical severity and phenotypic variability, onset symptoms are always present since the first year of age, although they can be mild.		1	5	5	2	13
	8%		92%			100%

Statement 2. Clinical phenotypes:

	1	2	3	4	5	TOT
2.1 It is necessary to raise awareness on underestimated symptoms, such as oculogyric crises, dystonia or dyskinesia.			2	4	7	13
	0%		100%			100%
2.2 The occurrence of hypoglycemic crises (non-diabetes-related) is not always recognized as a sign of metabolic dysfunction in AADC deficiency.			4	4	5	13
	0%		100%			100%
2.3 The identification of common AADC symptoms associated with recognition of hypoglycemic crises and additional non-neurological symptoms (dyarrhea, gastro-oesophageal reflux, feeding difficulties, nasal congestion) enables early diagnosis.			2	7	4	13
	0%		100%			100%
2.4 In early-onset forms, presentation with epileptic encephalopathy is rare and does not represent a typical clinical feature.			1	8	4	13
	0%		100%			100%

Statement 3. Diagnostic work-up:

	1	2	3	4	5	TOT
3.1 1 The analysis of CSF neurotransmitters profile should represent the first diagnostic step.		1	1	6	5	13
	8%		92%			100%
3.2 In adult-onset forms with mild phenotype (for which diagnosis is even harder) whole exome sequencing should be considered in the diagnostic work-up.			4	5	4	13
	0%		100%			100%
3.3 Based on the available evidence, venous 3-O-methyl-dopa (3OMD) levels represent a cheap, valid and readily available biomarker on which to base decision to begin diagnostic work-up for AADCd	1	1	3	5	3	13
	15%		85%			100%
3.4 Dosing plasma enzymatic AADC activity should be considered in cases with doubtful diagnosis if CSF neurotransmitters show non-significant abnormalities.			5	3	5	13
	0%		100%			100%

Statement 4. Regarding pharmacological and non-pharmacological therapies:

	1	2	3	4	5	TOT
4.1 Dopamine agonists, MAO inhibitors, and vitamin B6 currently represent the first therapeutic choice in AADC patients.			1	4	8	13
	0%		100%			100%
4.2 Anticholinergic drugs are commonly used for the symptomatic treatment of movement disorder. In some cases, for example status dystonicus or oculogyric crises, administration of benzodiazepines can become necessary.			3	6	4	13
	0%		100%			100%
4.3 The clinical management should be offered by a multi-disciplinary team (physical and occupational therapist, gastroenterologist, speech and language therapist, psychologist, clinical geneticist).			2	3	8	13
	0%		100%			100%
4.4 Early diagnosis is necessary in order to access gene therapy based on AAV vector, which is currently seeking approval by regulatory agencies.			2	4	7	13
	0%		100%			100%

Statement 5. Clinical network and support/advocacy groups:

	1	2	3	4	5	TOT
5.1 Awareness on AADC deficiency should be spread by involving scientific societies operating in pediatrics, child neurology and neurometabolics.			2	3	8	13
	0%		100%			100%
5.2 It is useful to increase awareness even outside clinical-scientific contexts by involving working groups dedicated to rare diseases in various Italian regions.			3	2	8	13
	0%		100%			100%
5.3 Based on the low number of patients in Italy, it is necessary to develop a dedicated working group for AADCd.			3	2	8	13
	0%		100%			100%
5.4 It is necessary to consider the opportunity to create a patients' association by means of a clinical network.		1	3	2	7	13
	8%		92%			100%

Statement 6. Follow-up:

	1	2	3	4	5	TOT
6.1 Cognitive and neuropsychological evaluation (appropriate for patient's age) should be performed by using standardized scales.			2	4	7	13
	0%		100%			100%
6.2 It is necessary to correctly characterize the associated movement disorder by means of standardized scales, according to patient's age (MD CRS 0-3; MD CRS 4-18R).			2	4	7	13
	0%		100%			100%
6.3 Standardized testing should be constantly applied during follow-up in order to evaluate treatment response, and cognitive and motor outcomes by using appropriate scales, as these data are lacking from the literature.			2	4	7	13
	0%		100%			100%
6.4 Improvements associated with cognitive and motor development and movement disorder severity after drug or gene therapy should be monitored by administering standardized scales.			2	3	8	13
	0%		100%			100%