AADCd
Deficit di decarbossilasi degli L-aminoacidi aromatici

AADC Deficiency Is a Rare, Inherited Disorder of Neurotransmitter Synthesis

AADC deficiency is an inborn error of neurotransmitter biosynthesis, with an autosomal-recessive inheritance resulting from pathogenic variants in the dopa decarboxylase gene, *DDC*, encoding for the AADC enzyme

Lack of the AADC enzyme leads to a severe combined deficiency of dopamine, serotonin, and other catecholamines (norepinephrine and epinephrine)

Key clinical symptoms include **hypotonia**, **movement disorders**, **severe neurologic dysfunction**, **failure to achieve any developmental milestones**, **failure to thrive**, **oculogyric crises**, and **autonomic symptoms**

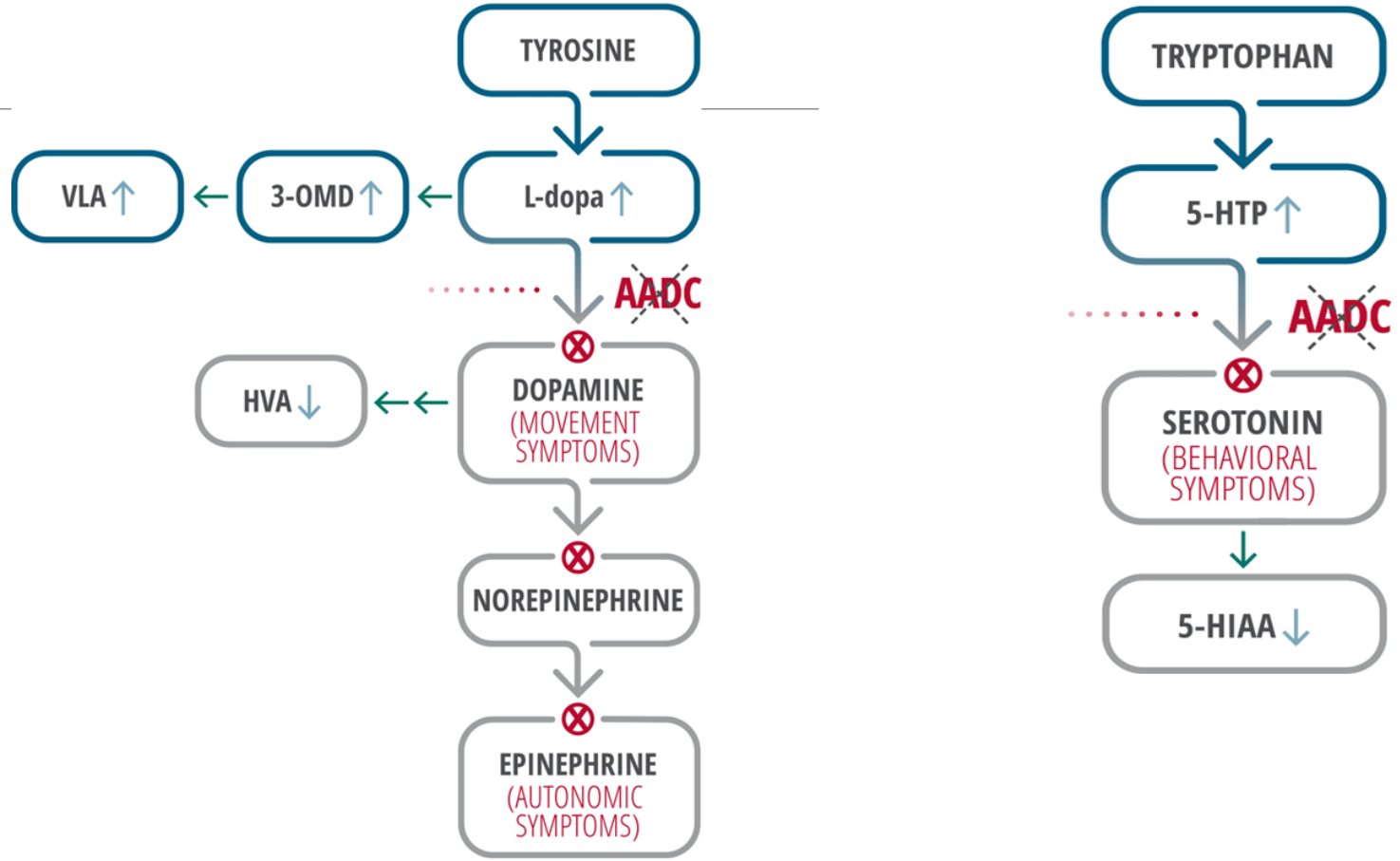
Patients typically present with symptoms of AADC deficiency within the first few months of life

Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12. doi:10.1186/s13023-016-0522-z.

Principali marcatori biochimici per il deficit di AADC

- Il deficit di AADC è caratterizzato da una ridotta sintesi di **ammine biogene**
- ↑ L-DOPA$_{(CSF)}$, ↑ 5-OH-Trp$_{(CSF)}$, ↑ 3-OMD$_{(CSF, plasma and DBS)}$
- ↓ HVA$_{(CSF)}$, ↓ 5-HIAA$_{(CSF)}$
- ↓ Noradrenaline$_{(plasma)}$, ↓ Serotonin$_{(blood)}$, ↓ Dopamine$_{(plasma)}$, ↓ Adrenaline$_{(blood)}$

Ridotta attività enzimatica nel plasma



3-OMD=3-O-methyldopa; 5-HIAA=5-hydroxyindoleacetic acid; 5-HTP=5-hydroxytryptophan; HVA=homovanillic acid; L-dopa=L-3,4-dihydroxyphenylalanine; VLA=vanillactic acid.

AADC, aromatic L-amino acid decarboxylase; 5-HTP, 5-hydroxytryptophan; L-DOPA, L-3,4-dihydroxyphenylalanine.

1. Himmelreich N, *et al. Mol Genet Metab.* 2019;127(1):12–22; 2. Wassenberg T, *et al. Orphanet J Rare Dis.* 2017;12(1):12; 3. Brun L, *et al. Neurology*. 2010;75(1):64–71.

AADCd Signs and Symptoms

COMMON

- Hypotonia (mainly truncal)
- Floppy infant
- Hypokinesia
- Bradykinesia
- Oculogyric Crises
- Neurodevelopmental Delay
- Ptosis
- Dystonia
- Excessive sweating

LESS COMMON

- Epileptic seizure
- Sleeping disorders
- Irritability
- Dysphoria
- Autistic Traits
- Instability of body temperature

NON- NEUROLOGICAL

- Diarrhea
- Feeding difficulties and body weight gain difficulties
- Nasal Congestion
- Gastroesophageal reflux
- Hypoglycemia (not related to diabetes)
- Hyperprolactinemia

Diagnostic Delays in Patients With AADC Deficiency

In the published consensus guidelines[1]

- Mean age of onset for patients with AADC deficiency is **2.7 months** (n=68)
- Despite this young age of symptom onset, the mean age of diagnosis is **3.5 years**[a] (n=68)

Because of similarities in clinical presentation with other conditions, AADC deficiency is often undiagnosed or misdiagnosed[2,3]

Potential misdiagnoses include[1,3,4]

- Cerebral palsy
- Movement disorders
- Mitochondrial disease
- Epilepsy
- Myasthenia gravis

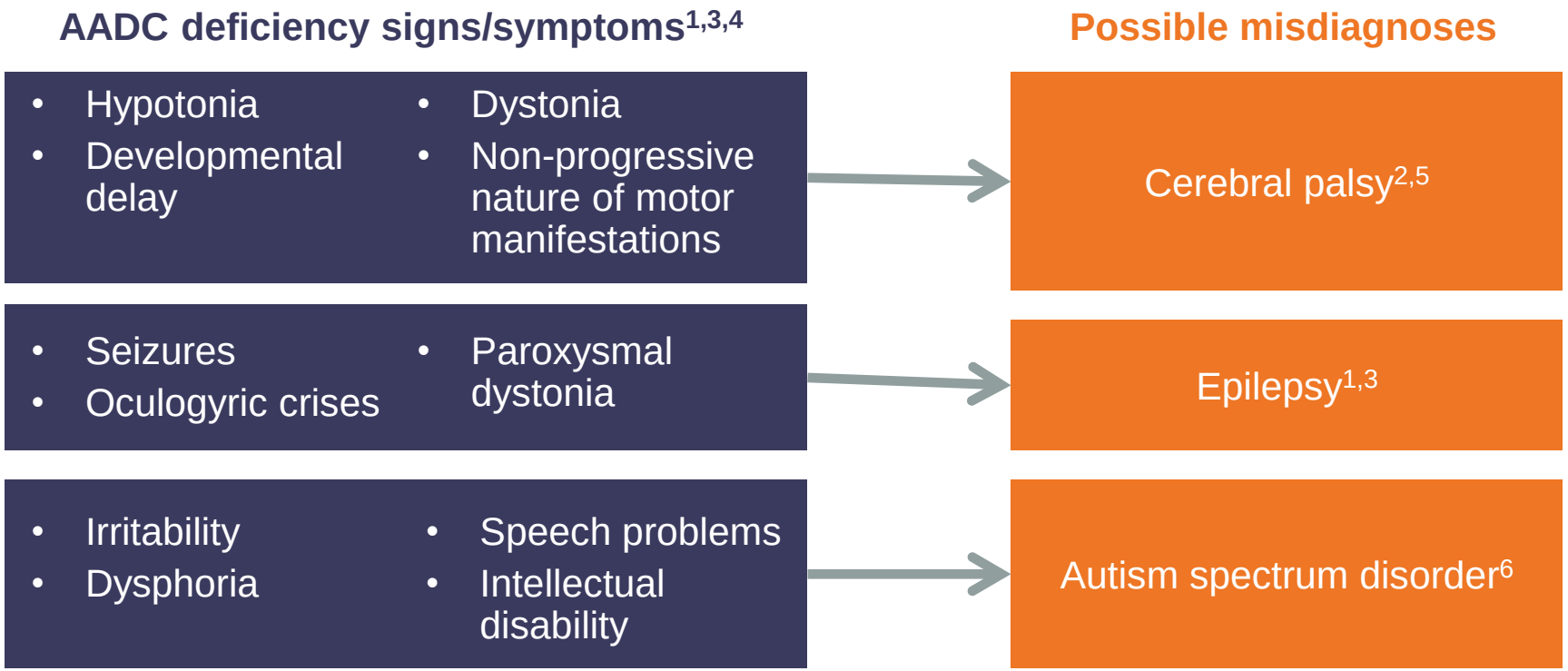
- Symptoms usually **appear within the first year of life**[1]
- The speed of the diagnostic process **varies by country and setting** depending upon access to specialists, geneticists and lab resource, awareness of the condition; inpatient vs outpatient; and logistics around testing[4,5]
- **Mean age of diagnosis is 3.5 years**,[a] but it can take anywhere from 3 months to multiple years from seeing a specialist to diagnosis

[a]Range: 2 months to 23 years.[1]

1. Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12. doi:10.1186/s13023-016-0522-z. 2. Pons R, et al. *Neurology.* 2004;62(7):1058-1065. 3. Helman G, et al. *J Inherit Metab Dis Rep.* 2014;17:23-27. 4. Atwal PS *Mol Genet Metab.* 2015;115:91-94. 5. Chien YH, et al. *Mol Genet Metab.* 2016;118(4):259-63.

AADC Deficiency May Present as Other Conditions

Due to similarities in clinical presentation with other conditions (e.g. cerebral palsy and epilepsy), patients with AADC deficiency are often undiagnosed or misdiagnosed[1–3]



AADC, aromatic L-amino acid decarboxylase.

1. Himmelreich N, *et al. Mol Genet Metab.* 2019;127(1):12–22; 2. Pearson TS, *et al. Mov Disord.* 2019;34(5):625–636; 3. Manegold C, *et al. J Inherit Metab Dis.* 2009;32(3):371–380; 4. Wassenberg T, *et al. Orphanet J Rare Dis*. 2017;12(1):12. doi:10.1186/s13023-016-0522-z; 5. Hallman-Cooper JL and Gossman W. StatPearls. Treasure Island, FL: StatPearls Publishing; 2019. https://www.ncbi.nlm.nih.gov/books/NBK538147 Updated July 18, 2019 (Accessed: November 2019); 6. Campisi L, *et al. British Medical Bulletin.* 2018; 127:91–100.

Agenda

- How is it Diagnosed?

Current Testing Landscape for AADC Deficiency

Screening Tests[1,2]	
Test	**Indicator of AADC Deficiency**
Urine organic acids	**Elevated** • Vanilpyruvic acid • 3-OMD (3-*O*-methyldopa, 3-methoxytyrosine) • N-acetylvanilalanine • Vanillactic acid
Plasma metabolite analysis	Marked elevation in 3-OMD

Confirmatory Tests[3] *	
Test	**Indicator of AADC Deficiency**
CSF neurotransmitter panel	**Low** • 5-HIAA, HVA, MHPG **Elevated** • 3-OMD, L-Dopa, 5-HTP **Normal** • Pterin levels
Genetic testing	Pathogenic mutation in *DDC* gene
Plasma enzyme assay	Low levels of AADC enzyme activity

***2 out of 3 core "Confirmatory Tests" should be positive to confirm AADC deficiency**

HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

1. Atwal PS, et al. *Mol Genet Metab*. 2015;115:91-94. 2. Gallagher RC, et al. Genet Med. 2018;20(7):683-691. 3. Wassenberg T, et al. *Orphanet J Rare Dis.* 2017;12(1):12. doi:10.1186/s13023-016-0522-z

Other Diagnostic Tests

MAGNETIC RESONANCE IMAGING (MRI) OF THE BRAIN	
Is the imaging helpful in the diagnosis of AADCd?	**Since there is no specific MRI pattern, imaging is NOT helpful in the diagnosis of AADCd.**
Is the imaging necessary?	**It is necessary in the work-up of a patient with neurodevelopmental delay to exclude other conditions in the differential diagnosis.**

ELECTROENCEPHALOGRAFY	
Is the EEG helpful in the diagnosis of AADCd?	**EEG is not needed to diagnose AADCd.** • EEG abnormalities, including slowing, fast activity, and poly-spikes, have been reported in some patients.
Is the EEG necessary?	**EEG can be used in the work-up of AADCd if there is a clinical suspicion of epilepsy to differentiate oculogyric crises from epileptic events, or in the general work-up of neurodevelopmental delay.**

- **Current Treatments**

Supportive treatments focus on treating the symptoms of AADC deficiency, yielding few improvements for many patients[1,2]

Pharmacologic treatment[2]

First-line treatment	Dopamine receptor agonists	MAO inhibitors	Pyridoxine (vitamin B6)
Additional symptomatic treatment	Anticholinergic agents	Melatonin	
	α-adrenoreceptor agonists	Benzodiazepines	
Special cases only*	L-DOPA without carbidopa		

Non-pharmacotherapy[2]

Therapy	Physical
	Occupational
	Speech
Supplements	Folinic acid

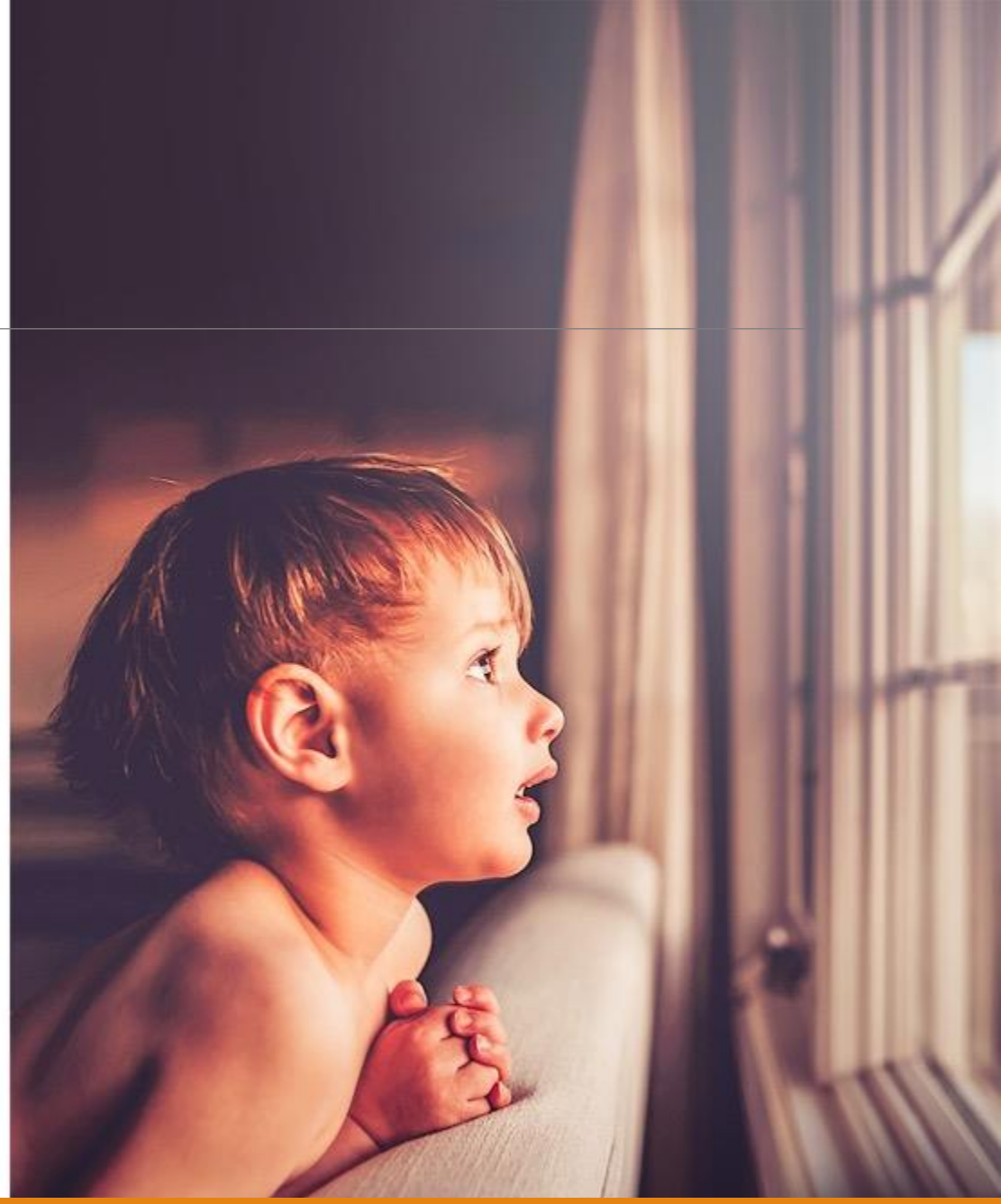
Recognition of AADC deficiency is paramount as some therapies are contraindicated and many drugs have antagonistic properties for neurotransmitters. Before initiating any drug, the potential benefits should be carefully considered[2]

*In patients with L-DOPA binding site mutations.
AADC, aromatic L-amino acid decarboxylase; L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase.
1. Chien YH, *et al. Lancet Child Adolesc Health*. 2017;1(4):265–273; 2. Wassenberg T, *et al. Orphanet J Rare Dis*. 2017;12(1):12.

Gene Therapy for AADC Deficiency

EMA Approval on July 2022

- Eladocagene Exuparvovec has been approved by EMA as FIRST Gene Therapy Treatment for AADCd directly infused into the putamen for patients aged 18 months or over.



La terapia genica per il deficit di AADC ora disponibile in Italia

Autore: Ilaria Vacca, 07 Dicembre 2023

Per il piccolo Simone è stato necessario l'intervento del Governo, ora finalmente la terapia è in commercio, per tutti i bimbi che ne avranno bisogno

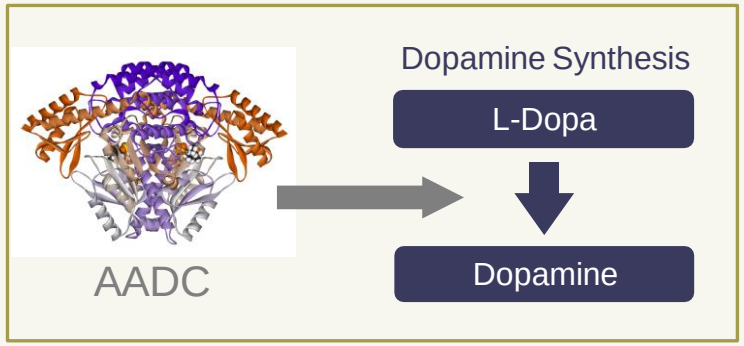
Una nuova e importante possibilità terapeutica è diventata una realtà concreta in Italia: la terapia genica per il deficit di decarbossilasi degli L-aminoacidi aromatici (AADC), una rarissima malattia neurometabolica ereditaria che causa una disabilità molto grave. Si tratta del farmaco eladocagene exuparvovec (nome commerciale Upstaza), di PTC Therapeutics, indicato per il trattamento di pazienti di età pari o superiore a diciotto mesi con una diagnosi di deficit di decarbossilasi degli L-aminoacidi aromatici (deficit di AADC) confermata dal punto di vista clinico, molecolare e genetico e con fenotipo severo. La determina in Gazzetta Ufficiale è del 20 novembre, che significa che **ora il farmaco è effettivamente disponibile per la pratica clinica.**

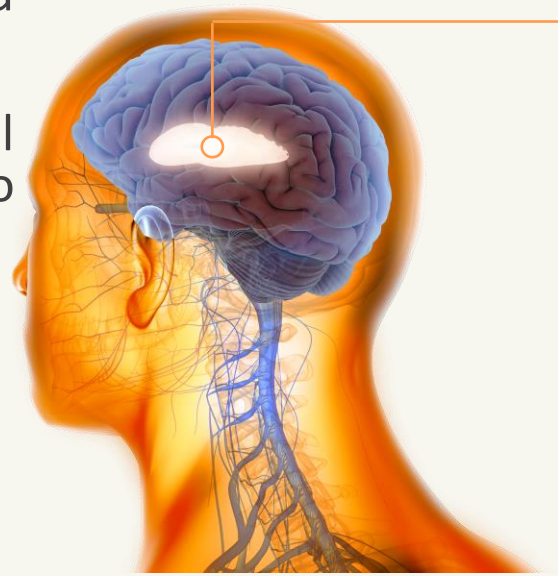
Il primo bambino ad essere trattato con questa terapia genica in Italia è stato Simone, che oggi ha 3 anni e mezzo e ha fatto grandi progressi. **Per lui è stato necessario l'intervento del Presidente del Consiglio e del Sottosegretario alla Salute** Marcello Gemmato, che dopo un appello della famiglia si sono mossi per trovare, insieme all'Agenzia Italiana del Farmaco e al Policlinico Umberto I una soluzione veloce per lui, poiché a giugno, quando il bimbo ha ricevuto l'infusione della terapia - un'infusione da praticare direttamente nel cervello – il farmaco non aveva ancora completato il suo iter approvativo in Italia. La terapia, che però si era già dimostrata sicura ed efficace, avendo superato il vaglio di EMA e ottenuto l'approvazione della Commissione Europea, era già stata usata con successo su altri bambini, e la situazione di Simone non consentiva di attendere i tempi necessaria al completamento della procedura.

Gene Therapy for AADC Deficiency

The DDC gene, which codes for AADC, is delivered by a recombinant adeno-associated virus (AAV) vector serotype 2 (AAV2).

The AAV2 vector is injected through bilateral putamen injection by stereotactic surgery to achieve long-term transgene expression[2,3,4].





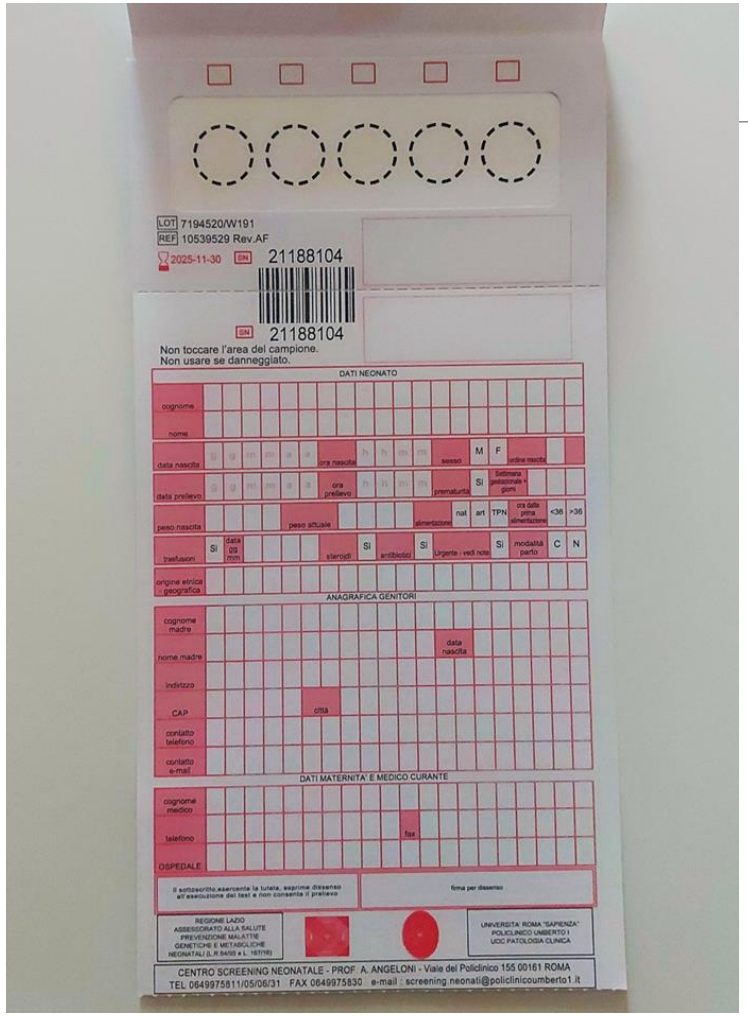
Putamen

- ✓ The major site of AADC activity in the brain
- ✓ Affected cells remain intact for long periods
- ✓ Belongs to the «motor loop»in the corticostriatal connections related to motor performance
- ✓ Limited, focal number of affected cells
- ✓ Amenable to direct local delivery[4]
- ✓ History of AADC gene therapy injections in Parkinson's disease[5,6]

1. Gene Therapy for the Treatment of AADC Deficiency. Available at: https://ncats.nih.gov/trnd/projects/active/aadc-deficiency (last accessed April 2019); 2. Lee NC et al. *Hum. Gene Ther*. 2014;25:189-198; 3. Chtarto A et al. *Br J Clin Pharmacol*. 2013;76:217-232; 4. Hwu WL et al. *Sci Transl Med*. 2012;4:134ra61; 5. Christine CW et al. *Neurology*. 2009;73:1662-1669; 6. Muramatsu S et al. *Molec Ther*. 2010;18:1731-1735

Progetto Screening metabolico 3-OMD e 5-HTP DBS cards

DBS cards kit



The technique is non-invasive, simple and rapid

Il KIT include:

- DBS card
- Flyer istruzioni
- Form Consenso Informato e scheda raccolta dati
- Busta di carta che conterrà quanto elencato sopra e che sarà ritirata dal corriere DHL dopo prenotazione tramite telefono e/o sito internet DHL

Conclusions

Summary

AADC deficiency is an inborn error of neurotransmitter biosynthesis, with an autosomal recessive inheritance resulting from pathogenic mutations in the *DDC* gene that codes for the AADC enzyme[1]

- Based on calculations of presumed prevalence **>90% of cases of AADC deficiency are undiagnosed**[2]

Key symptoms include hypotonia, oculogyric crises, dystonia, hypokinesia, **developmental delay**, and autonomic symptoms that include ptosis, excessive sweating, nasal congestion and hypotension[2,3]

- **AADC deficiency should be tested for in children presenting with these unexplained symptoms**[3,4]
- May present as cerebral palsy or epilepsy mimic[2,5]

Diagnostic testing for AADC deficiency includes plasma AADC activity testing, CSF metabolite testing and genetic testing[3]

- 2/3 test results should be positive before a diagnosis is made[2]

Current treatment options include dopamine agonists, MOA inhibitors, and pyridoxine or its active form[3]

- Patient response to dopaminergic medications is variable and evidence is of low quality[3,6]
- **Gene therapy** options to replace the mutated *DDC* gene by AAV-mediated gene transfer are now available

Prompt and accurate diagnosis of patients with AADC deficiency may enable earlier access to appropriate management options[2]

DDC, dopa decarboxylase; CSF, cerebrospinal fluid; MAO, monoamine oxidase; AAV, adeno-associated virus.

1. Chien YH, *et al. Mol Genet Metab*. 2016;118:259–263; 2. Himmelreich N, *et al. Mol Genet Metab.* 2019;127(1):12–22; 3. Wassenberg T, *et al. Orphanet J Rare Dis*. 2017;12:12; 4. Pearson TS, *et al*. *Mov Disord* 2019;34:625–636; 5. Ito S, *et al. Dev Med Child Neurol.* 2008;50:876–878; 6. Brun L, *et al. Neurology.* 2010;75:64–71; 7. Hwu WL, *et al. Sci Transl Med.* 2012;4:134ra6.

Grazie per l'attenzione