Key developments in the diagnosis, treatment and understanding of childhood-onset, treatment-resistant epilepsies

Highlights from the AES 2020 Virtual congress

A touchCONFERENCE expert interview recorded in December 2020

AES, American Epilepsy Society.

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Disclosures

- Dr Coppola has received consultancy fees from Eisai and GW Pharmaceuticals, and received travel sponsorship from UCB

Biography

- Dr Coppola is Assistant Professor of Neurology at the Department of Neuroscience, Reproductive and Odontostomatological Sciences at the University of Naples Federico II, Italy
- She is a member of the Italian chapter of the ILAE
- Her main area of expertise is the diagnosis and treatment of genetically determined epilepsies
- She has authored about 100 peer-reviewed articles and book chapters

ILAE, International League Against Epilepsy.

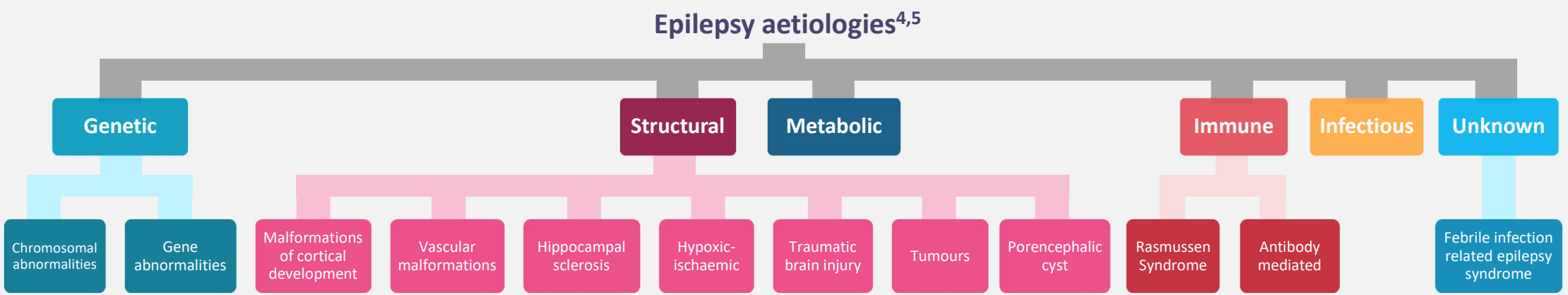
Learning Objectives

- Recognise the unmet needs and challenges that remain for people living with childhood-onset, treatment-resistant epilepsies.
- Understand the challenges that remain in the management and monitoring of the childhood-onset epilepsies, and be aware of the key diagnostic advances presented at AES 2020.
- Describe the key therapeutic developments for childhood-onset, treatment-resistant epilepsies presented at AES 2020.

Is treatment resistance to conventional anti-epileptic medicines a common problem, and does it affect specific epilepsies more than others?

Limitations of current ASMs

- Despite the availability of many ASMs, 30–40% of people with epilepsy have refractory disease[1]
- Certain conditions tend to be more refractory to treatment than others, including ***developmental or progressive*** epilepsies with a genetic aetiology, ***structural*** epilepsies with lesions or brain malformations (rare finding), and ***immune conditions*** such as autoimmune encephalitis[2,3]



ASM, anti-seizure medication.

1. Laxer KD, et al. The consequences of refractory epilepsy and its treatment. *Epilepsy Behav.* 2014;37:59–70; 2. Jain P, et al. Diagnosis and management of epileptic encephalopathies in children. *Epilepsy Res Treat.* 2013;2013:501981; 3. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. *J Clin Neurol.* 2016;12:1–13; 4. www.epilepsydiagnosis.org/ (accessed 8 December 2020); 5. Scheffer IE, et al. ILAE Classification of the Epilepsies Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58: 512–21

How has the understanding of childhood-onset epilepsies evolved in recent years, and what are the key areas for current and future research?

Understanding of childhood-onset epilepsies has evolved substantially in recent years

- In recent years, advances in genetics, imaging, neurophysiology and therapeutics have dramatically increased our understanding of childhood-onset epilepsies; key advances include:

DEE[1,2]

- This spectrum of rare disorders is characterised by early-onset, refractory seizures
- Individuals with DEE have high rates of comorbid conditions, including intellectual disability, autism spectrum disorder, and behavioural problems

Co-existence of epilepsy with movement disorders[3,4]

- Occurs in up to 40% of people with a rare genetic epilepsy variant; examples include:
  - *TBC1D24* (epilepsy with dystonia)
  - *SCN1a* gain of function (dyskinesia)
- Some epilepsy treatments may not be effective in the presence of a movement disorder
- May require different diagnostic algorithms and alternative monitoring tools (eg video)

Surgery[5]

- It is now established that early surgery in young people with epilepsy can:
  - Lead to earlier discontinuation of ASMs
  - Improve long-term cognitive outcomes and minimise long-term comorbidities

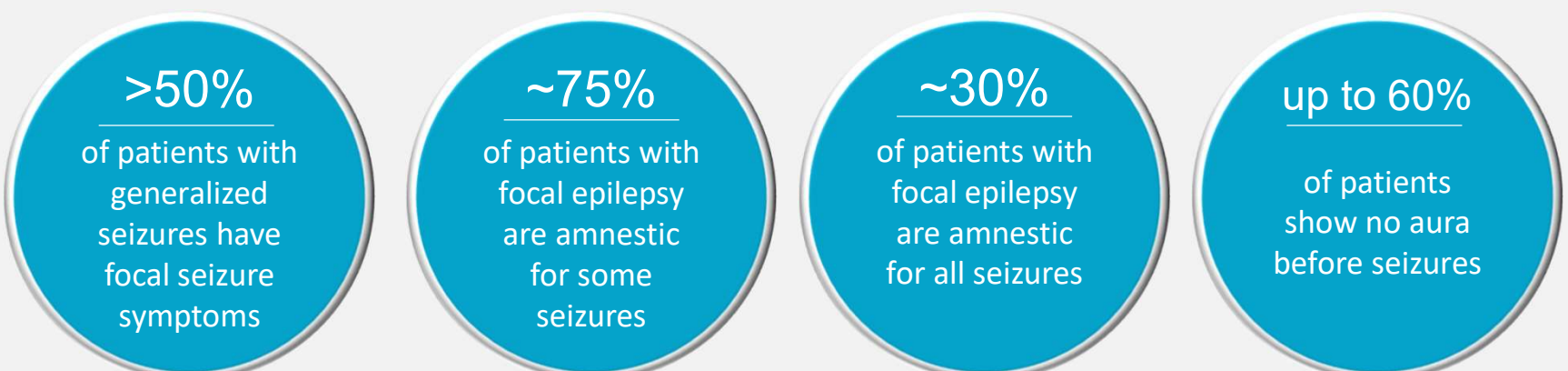
DEE, developmental epileptic encephalopathy.

1. Scheffer IE, et al. ILAE Classification of the Epilepsies Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58: 512–21; 2. Scheffer IE, et al. Deciphering the concepts behind "Epileptic encephalopathy" and "Developmental and epileptic encephalopathy". *Eur J Paediatr Neurol.* 2020;24:11–4; 3. Guerrini R. Genetic epilepsies associated with movement disorders. Presented at the virtual AES congress 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762552 (accessed 6 Jan 2021); 4. Zuberi S. Approach to the evaluation of a patient with epilepsy and movement disorders. Presented at the virtual AES congress 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762552 (accessed 6 Jan 2021); 5. Braun K. Early surgery to improve outcomes and cognition. Presented at the https://aes2020.hubb.me/fe/schedule-builder/sessions/762531 (accessed 7 Jan 2021).

In your opinion, what were the most promising advances in the diagnosis and monitoring of childhood-onset, treatment-resistant epilepsies presented at AES 2020?

Challenges in the diagnosis of epilepsy

- Determining the type of epilepsy is critical for prognosis and treatment selection
- Considerable overlap between the different types of seizure makes diagnosis challenging



Bank AM, et al. Diagnosis and management of new onset epilepsy in adults. *US Neurology*. 2020;16:32–7.

Promising advances in the diagnosis and monitoring of childhood-onset treatment-resistant epilepsies

- Many advances were presented at the AES 2020, from genetic diagnostics to imaging and monitoring devices

Diagnosis

- Identification of new disease-associated genes, including:[1]
  - Mosaicisms leading to brain malformations[2]
  - Repeat expansions disorders[3]
  - Polygenic factors
  - Risk burden

Monitoring[4,5,6]

- Wearable devices for long-term EEG monitoring, e.g. an EEG patch
- Video tools to help identify convulsive seizures
- Eyeglasses to help identify absence seizures
- Data remotely accessible to clinicians

EEG, electroencephalogram.

1. Weckhuysen S. Genetics of epileptic encephalopathy and expression. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762531 (accessed 7 Jan 2021); 2. Poduri A. Mosaicism in human epilepsy. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762521 (accessed 18 Jan 2021); 3. Bahlo M. Identification of repeat expansions with whole exome and whole genome sequencing in epilepsy patients. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762521 (accessed 18 Jan 2021); 4. Kessler S, et al. Pediatric epilepsy clinical trials: current and future challenges. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762559 (accessed 18 Jan 2021); 5. Beniczcky S. Automated seizure detection using wearable devices. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762559 (accessed 18 Jan 2021); 6. Ryvlin P, et al. EEG: ultra-long-term seizure identification devices. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762599 (accessed 18 Jan 2021).

In your opinion, what were the most promising therapeutic developments for childhood-onset, treatment-resistant epilepsies presented at AES 2020?

Gene replacement therapies*

- Gene replacement therapies are among the most exciting new developments for childhood-onset treatment resistant epilepsies[1]

AAV[1]

- Involves replacement of the entire gene using an AAV vector
- Not suitable for large genes, such as *SNC1a*
- Likely to require intrathecal administration

ASO[2]

- Small DNA sequences able to bind RNA and influence processes such as translation, splicing, and protein degradation

NMD[1]

- Approach that blocks gene-suppressing exons to promote specific gene transcription (eg for *SCN1a*)

CRISPR[2]

- Used to activate specific promoters and increase gene expression

*Currently in preclinical development; no therapies are currently approved for childhood onset TREs.
AAV, adeno-associated vector; ASO, antisense oligonucleotide; CRISPR, clustered regularly interspaced short palindromic repeats; NMD, nonsense mediated decay.
1. Carvill G. Gene modifying therapy. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762553 (accessed 18 Jan 2021); 2. McTague A. Medical modification of disease expression and encephalopathy. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762531 (accessed 7 Jan 2021).

How do you think these developments might address some of the remaining unmet needs in these patient populations?

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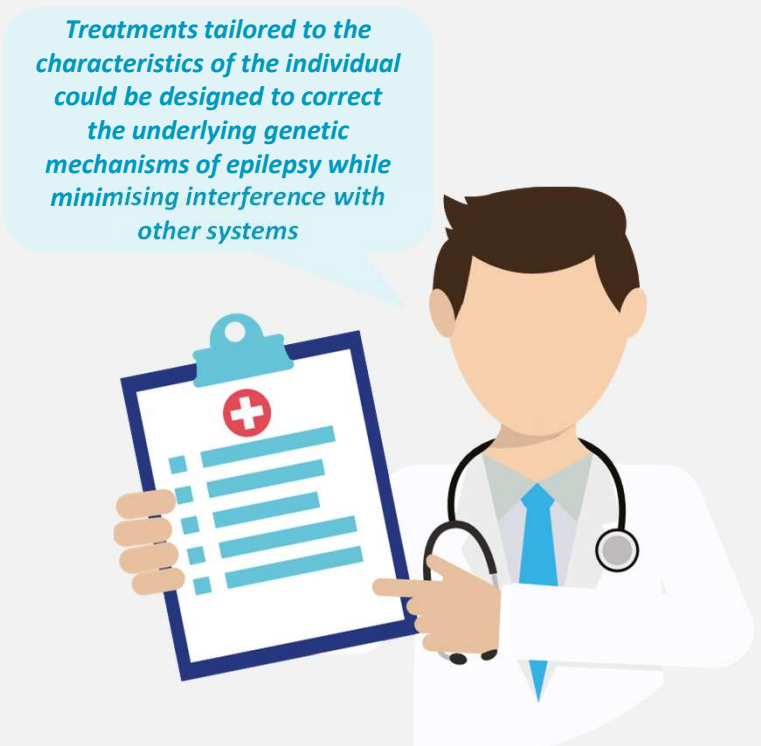
Personalised treatment may be key to addressing current unmet needs

- There are still unmet needs in childhood-onset epilepsy:
  - Many conditions are commonly resistant to current treatments[1]
  - While there are many ASMs available, these are not able to prevent or cure epilepsy[2]
- Advances in genetic technology and precision medicine may allow us to focus on the underlying mechanisms responsible for seizures, e.g.
  - Ketogenic diet with betashot in patients with GLUT-1 deficiency[3]



1. Jain P, et al. Diagnosis and management of epileptic encephalopathies in children. *Epilepsy Res Treat.* 2013;2013:501981; 2. NHS. Treatment: epilepsy. Available at https://www.nhs.uk/conditions/epilepsy/treatment/ (accessed 6 Jan 2021); 3. McTague A. Medical modification of disease expression and encephalopathy. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762531 (accessed 7 Jan 2021).

How has patient care and support for people with childhood-onset epilepsies been affected by the COVID-19 pandemic?

COVID-19, epilepsy and the risk of infection and seizures

- To date, there is no evidence that:[1]
  - Having epilepsy increases the risk of contracting COVID-19
  - Having epilepsy weakens the immune system
  - Having epilepsy increases the risk of being more severely affected by COVID-19
  - ASMs increase the risk of COVID-19 infection
- Infection, fever (especially in children), sleep deprivation and generally being unwell are known triggers, but there is also no evidence that COVID-19 can directly trigger a seizure[1]
- Additional factors, such as stress, reduced physical activity and social isolation may also impact the health of people with epilepsy[2,3]

1. Sander L. Epilepsy society: Epilepsy and the coronavirus (COVID-19) FAQs. www.epilepsysociety.org.uk/epilepsy-and-coronavirus-covid-19-faqs (accessed 8 December 2020); 2. Hall G, *et al.* A tale of two pandemics: How will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another? *Prog Cardiovasc Dis. 2020;* https://doi.org/10.1016/j.pcad.2020.04.005 (accessed 11 December 2020); 3. Rosengard JL, et al. Seizure control, stress, and access to care during the COVID-19 pandemic in New York City: The patient perspective. Epilepsia. 2021;62:41–50.

Care and support for people with epilepsy during the COVID-19 pandemic

- The COVID-19 pandemic has changed approaches to care and support for people with epilepsy (and their caregivers)
- Telemedicine, in particular, has been widely implemented to enable remote clinician follow-up[1]
- At the AES 2020, a new video tool developed by NHS Scotland (V-create) was headlined that enables families to upload home video for clinicians to review[2]
  - V-create can help improve the clinician's ability to remotely identify different types of epileptic seizures, non-epileptic paroxysmal seizures and movement disorders

NHS, National Health Service.

1. Rossi M. Tips and tricks for the telehealth visit in epilepsy. Presented at the virtual AES congress 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762530 (accessed 18 Jan 2021); 2. Zuberi S. Approach to the evaluation of a patient with epilepsy and movement disorders. Presented at the virtual AES congress 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762552 (accessed 6 Jan 2021).

Considering any new evidence presented at AES 2020, what is the current outlook for patients with childhood-onset, treatment-resistant epilepsies, and how might we further improve their quality of life?

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Improving patient outlook and quality of beyond diagnostic and therapeutic improvements

- Beyond diagnosis and treatment, the quality of life of people with epilepsy, as well as their caregivers, is an important therapeutic goal – key improvements in this area include:
- ***Wearable devices*** to identify types and severities of seizures, especially during sleep, and potentially reduce the risk of SUDEP[1,2]
  - Bracelets including accelerometers
  - Surface EMG detectors
  - Combined approaches (accelerometer + heart rate + electrodermal activity)
- ***Portable EEG*** devices (e.g., the EEG patch), applied behind the ear pavilion or under the hair to enable long-term EEG monitoring at home

SUDEP, sudden unexpected death in epilepsy.

1. Epilepsy Society. SUDEP. Available at https://epilepsysociety.org.uk/living-epilepsy/sudep (accessed 07 Jan 2021); 2. Beniczcky S. Automated seizure detection using wearable devices. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762559 (accessed 18 Jan 2021); 3. Friedman D, et al. EEG: ultra-long-term seizure identification devices. Presented at the virtual AES 2020. Available at https://aes2020.hubb.me/fe/schedule-builder/sessions/762599 (accessed 18 Jan 2021).

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