9th Europaediatrics
13-15 June
Dublin, Ireland 2019

Meet the Expert Mini-Reviews

EUROPEAN PAEDIATRIC ASSOCIATION (EPA / UNEPSA)

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

9th Europaediatrics
13-15 June
Dublin, Ireland 2019

Friday 14th June
Saturday 15th June
08:00-08:45

Meet the Expert 1 – Diagnosis and management of seizures in infants and children
Liffey A

Professor Mary King and Dr Sophia Varadkar

Epilepsy is a disease of the brain characterised by seizures. It is common, with an estimated prevalence of active epilepsy of 5-10/1000. Paediatric epilepsy offers particular challenges in terms of diagnosis, evaluation and management.

Diagnosis

Epilepsy is not just one condition. The 'Epilepsies of Childhood' are not usually missed, clinicians are more likely to forget the other possibilities (fewer than 25%, of all children in whom epilepsy is considered, will actually have an epilepsy). Making the diagnosis can be challenging and misdiagnosis rates are high, up to 15%. The impact of misdiagnosis includes anxiety, stigma, inappropriate/over-medication, adverse events, inappropriate educational or social management and missed opportunities to treat another condition, most importantly cardiac.

The diagnosis is made on the clinical history. An account of the event from both the child/young person and any eye-witness is needed. Investigations may help but there is no one investigation that confirms or rules out the diagnosis. The ease of capturing events on parental mobile phones has greatly helped and is now an important diagnostic tool. Electroencephalography (EEG) may lend support to the diagnosis, help determine seizure type and define epilepsy syndrome. EEG should always include video and is more correctly termed video-EEG. It should include photic stimulation and hyperventilation. Capturing sleep also increases the diagnostic yield. Long-term monitoring or ambulatory/home video-EEG may be helpful in diagnostic uncertainty. Magnetic resonance imaging (MRI) is the standard in neuro-imaging, identifies structural abnormalities causing epilepsy and while not routinely required after a first suspected seizure in childhood, it should be undertaken in all children presenting before the age of two-years, in all with a suggestion of a focal onset on history, examination or EEG and in all children who do not respond to first-line medication.

Treatment Aim and Expectation

The treatment aim is seizure freedom. Anti-epileptic drugs are the main-stay of treatment. Seizure freedom is achieved with the first anti-epileptic drug (AED) in 58-70% of children and with the second drug in a further 10-20%. Pharmacoresistant epilepsy is defined as failure of adequate trials of two tolerated appropriately chosen and used AED schedules (monotherapy or combination) to achieve seizure freedom.

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Pharmacoresistance should prompt a review of the diagnosis, the seizure type(s) and epileptic syndrome (is the right drug being used for the seizure type and syndrome) and compliance. There are many causes and many different types of epilepsies. Recognising this is key to understanding the reasons for failure of treatment.

Seizure Types, Epilepsy Type, Epilepsy Syndromes and Causes of the Epilepsies

The epilepsies are considered in three levels – starting with seizure type (described by the first feature of the seizure), then epilepsy type (focal, generalised, combined generalised and focal and unknown), with these elements, the clinical features, signs, and symptoms, age of onset, specific EEG characteristics and aetiology then coming together to make a distinctive, recognisable clinical disorder, termed the electro-clinical syndromes. The newer ILAE 2017 classification

The most recent International League Against Epilepsy (ILAE) 2017 classification has been updated to reflect our evolving understanding of the causes of epilepsies, with newer imaging, immunology and genetic investigations. Aetiology is described in six categories: structural, genetic, infectious, metabolic, and immune and unknown. Next generation sequencing epilepsy genetic panels have completely changed our approach to the diagnoses of epilepsies, and the Early Infantile Epileptic Encephalopathies in particular. Yet despite all the recent advances there remains a significant number of children for whom the cause of their epilepsy is still unknown; this deserves regular reconsideration throughout a child's journey through to adulthood). Considering the causes of a child's epilepsy in this way is important as it informs the therapeutic options.

Treatment options in pharmacoresistant epilepsies

When the first two AEDs have failed, the chances that the next drugs will achieve seizure freedom are dramatically decreased. There should be prompt consider of other therapeutic options in pharmacoresistant epilepsies.

The main non-drug therapies should no longer be consider a last resort. These are the ketogenic diet, epilepsy surgery, and neurostimulation, most typically Vagus Nerve Stimulation (VNS) therapy.

The ketogenic diet is high fat, low carbohydrate diet, which is an effective treatment for epilepsy, with at least 50% response and an important early intervention in infants and younger children. It remains effective in older children and young people and less strict diets may be better tolerated.

Epilepsy surgery is a safe and effective management strategy in selected patients. Epilepsy surgery removes, disconnects or ablates brain parenchyma assumed to generate ictal epileptic (seizure) activity with the primary aim of alleviating seizures. Secondary aims may include neuro-developmental gains and behavioural improvement. Pre-surgical evaluation (PSE) should be in a centre with expertise in epilepsy surgery for children. PSE determines the area of ictal onset, and also delineates and minimises the risk of inflicting new deficits. For all-comers, the rates of seizure freedom are about 70%. There is no minimum age and indeed best seizure and cognitive outcomes are expected in younger children. Newer surgical treatments include Laser interstitial Thermal therapy (LiTT) for hypothalamic hamartoma.

Neuromodulation is the alteration of nerve activity through application of electrical or pharmaceutical agents. This may involve the central or peripheral nervous system. The delivery is through implanted or transcutaneous devices and the therapy is reversible as opposed to ablative or resective (stimulation rather than destruction). VNS therapy utilises repeated electrical stimulation of the efferent left Vagus nerve by a pulse generator device, ramped up stepwise over months. To date more than 100.000 patients have been treated with VNS world-wide with

approximately 2/3 of patients experiencing more than 50% seizure reduction. The newer responsive VNS systems use ictal-tachycardia detection as a biomarker of seizure onset and automatically deliver additional stimulation on detection to abort the seizure.

Novel therapies and Precision Medicine

Drug discovery and novel therapies seek to identify new targets. There is great interest in Cannabis-based Medicinal Products. Precision Medicine considers the scientific basis that underpins personalisation of care and targets the basis of disease. Rapid progress in epilepsy gene discovery and animal and in-vitro models tailored to genetically defined subtypes of epilepsy are allowing the development of medications and clinical trials of targeted therapies. In the genetic epilepsies, potential targets are the underlying molecular mechanisms, abnormal proteins or disrupted pathways and repurposing (fortuitous/coincidence drugs approved for other indications) and revisiting old drugs. Successes in treatable metabolic epilepsies and the epileptic encephalopathies/ion channel epilepsies, new horizons in NMDA antagonism and mTORopathies are encouraging, but we still have a long way to go.

Treatment of comorbidities

Comorbidities are important as they are frequent and treatable. Motor disorders, cognitive/learning difficulties, behavioural problems, autism, attention deficit hyperactivity disorder, and psychiatric diagnoses should be actively looked for and actively treated.

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Meet the Expert 2 - End of life guidelines/toolkit
Wicklow Hall 2

Dr Mary Devins and Dr Joanne Balfe

This workshop aims to provide practical advice and guidance for pediatricians caring for children at end-of life (EOL).

“Palliative care for children and young people with life-limiting conditions is an active and total approach to care, embracing physical, emotional, social and spiritual elements. It focuses on the enhancement of quality of life for the child and support for the family and includes the management of distressing symptoms, provision of respite and care through death and bereavement”. ACT/RCPCH, UK 2003.

Sadly, some children are born with or develop illnesses, which are life-limiting. Technological advances and improvements in neonatal and intensive care have led to an increase in the prevalence of children with life-limiting conditions. Despite this, the integration of children’s palliative care education into undergraduate and postgraduate medical education remains a challenge. A recent survey of Pediatricians in Ireland identified a paucity of experience and training in this vital topic and respondents reported significant interest in learning about symptom management, end-of-life care and advanced care planning.

In this workshop, we will use case presentations to help to illustrate some of the challenges in managing children at EOL . Practical advice will be given to help pediatricians in caring for children including calculating drug doses in syringe drivers.

Links to useful resources, answer questions and direct attendees to further educational programmes and events where available will be provided.

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CASE 1:

P is an 8 year old boy who weighs 25kg.

He was diagnosed at age 6 years with an Ewing Sarcoma of his Femur, presenting with persisting pain after a minor injury.

The tumour was large at diagnosis with poor prognostic indicators on work up.

P received chemotherapy followed by limb salvage surgical removal of residual tumour. Histology of the surgically removed tumour showed poor chemotherapy response. P had further chemo and radiotherapy and then proceeded to high dose chemotherapy and autologous stem cell transplant.

Sadly, within months of his transplant P presented with moderate leg pain and a limp. He had local tumour recurrence and inguinal lymph nodes, which were positive for metastatic tumour.

P's oncologist met with his parents and explained that P's prognosis was poor.

P's parents in conjunction with his oncologist elected to continue with further chemotherapy and radiotherapy to the affected inguinal region.

In view of the poor prognosis and pain P was referred to the Paediatric palliative Care Team for ongoing support and symptom management. On assessment P had 2 types of moderate to severe pain; a deep dull ache in his thigh which he found difficult to localise and a "fizzing", shooting pain which radiated down his leg.

P is commenced on an oral Opioid (Morphine) for his bone pain.

"Although there are a limited number of analgesic medicines that can be safely used in children, it is still possible to provide adequate analgesia with a two-step approach. This two-step strategy consists of a choice of category of analgesic medicines according to the child's level of pain severity: for children assessed as having mild pain, paracetamol and ibuprofen should be considered as first options and in children assessed as being in moderate to severe pain, the administration of an opioid should be considered".

Codeine is a 'weak' opioid which is no longer recommended in the management of pain in children. This is due to now well-known safety and efficacy problems related to genetic variability in biotransformation.

Morphine is the recognised first choice opioid in the management of moderate to severe pain in children. This is due to its demonstrated efficacy and relative safety plus expert opinion.

P was commenced on an adjuvant (Gabapentin) for his neuropathic pain.

There is little evidence regarding the management of neuropathic pain in children (cancer or non-cancer). First line medications such as NSAIDs, opioids, low-dose tricyclics, and gabapentinoids, appear to be successful treatment strategies. In a recent study both Gabapentin and Amitriptyline appear to be safe and effective in treating paediatric patients in the first-line treatment of Complex Regional Pain Syndrome Type I and neuropathic pain over a 6-week period. They both significantly decreased pain intensity scores and improved sleep plus both were equally safe.

Over the following months, P gradually deteriorated and began to complain of dyspnoea. On assessment his tumour had progressed further, he had developed multiple lung metastases and some intracranial lesions.

A joint decision between P, his parents and his oncologist was made to forgo any further chemotherapy and to focus on quality-of-life (QOL). P wanted to remain out of hospital and be at home if at all possible. His parents' wish was to care for him at home at end-of-life.

P and his parents were advised regarding the use of as required (PRN) low dose Opioid and Benzodiazepines for the relief of dyspnoea.

Studies regarding the use of opioid for dyspnoea are lacking in children.

There have, however, been a number of studies in adults suffering from various medical conditions causing dyspnoea including advanced cancer, cardiac and lung disease. These studies demonstrate improvement in refractory dyspnoea with morphine sulphate, without development of respiratory depression. The American College of Physicians recommends treating dyspnoea in adults with short-acting opioids. Expert opinion plus experience demonstrates similar benefits in treating children with dyspnoea. Other useful interventions include cool air from a fan or open window directed at the face, repositioning, a trial of oxygen, hypnosis or other relaxation techniques, and low dose PRN benzodiazepines for associated anxiety.

P had good QOL at home for a number of months but then he began to deteriorate dramatically. He became profoundly symptomatic from a dyspnoea perspective. He was also lethargic and weak. Assessment revealed bilateral pleural effusions.

P was unable to tolerate his medications via the enteral route and it became clear to his parents and his medical/nursing/AHP team that he was entering the final stages of his illness.

P's parents had already completed an 'Advanced care Directive' for him and also requested that his effusions be managed conservatively if at all possible to allow them to continue to care for him at home.

P was commenced on a subcutaneous (SC) infusion of medications including opioid and benzodiazepine.

PRN medications for possible pain, dyspnoea, seizures, increased secretions, agitation and nausea were made available via the SC route.

He died peacefully at home 7 days after he commenced on the syringe driver.

CASE 2

M is a 8 year old girl with severe neurological impairment (SNI) secondary to neonatal encephalopathy. She has gross motor functional score (GMFCS) 5 cerebral palsy, epilepsy and intellectual disability. M had a percutaneous endoscopic gastrostomy (PEG) tube placed at 12 months of age and is exclusively enterally fed.

Between age 5 and 6 years, M was admitted twice to paediatric intensive care (PICU) with pneumonia, which was managed with IV antibiotics and non-invasive ventilatory support. Following the second PICU admission, M's paediatrician, concerned about the possibility of future acute life-threatening events, met with her family to discuss their goals and wishes in the event of future health deterioration. M's family spoke about their wish to keep M as well as possible for as long as possible and to care for her at home.

It is known that over 57% of admissions to and 73% of deaths in PICUs the UK are for children with life-limiting conditions. An admission to PICU indicates a risk of future life-threatening event and should prompt paediatricians to engage in advance care planning discussions with the family. A shared decision making model, in which the healthcare professionals provide evidence and available medical options and the beliefs and preferences of the child and family are considered in determining the best –interests of the child is helpful. The Wishes Document provides a useful framework, which aims to support proactive planning including the wishes of the child and family.

At 7 years of age, M presented with increasing episodes of irritability and upset which parents attributed to gastrointestinal discomfort, they reported crying when feeds commenced. A number of investigations were performed to exclude a treatable cause for the GI discomfort including, abdominal ultrasound to assess for renal or gallstones, bloods including amylase, hip x-ray and dental review. All investigations were normal. A diagnosis of visceral hyperalgesia was made and M was commenced on Gabapentin very good effect.

Pain is frequently reported in children with SNI and it is essential that reversible and treatable causes of pain are excluded. Hauer and Houtrow's 2017 article provides a very useful guide to the assessment and management of pain in children with SNI . Visceral hyperalgesia is an increased

perception of pain in response to normal gastrointestinal sensory stimulus and is common in children with SNI. Neuropathic pain agents such as Gabapentin can be useful in managing the pain of visceral hyperalgesia.

Unfortunately after 6 months, M presented again with increasing irritability and feed intolerance. Parents reported distress with crying, gagging and sweating once feeding commenced. Symptoms improved when feeds were discontinued. Peripheral oedema was noted. M was admitted to hospital and commenced on IV fluids with good resolution of symptoms, but on reintroduction of enteral feeds symptoms recurred.

Non-ambulant children with severe neurological impairment may have significantly lower calorific and fluid requirements than typically developing children. If an empiric trial of medications has failed to fully manage symptoms, it is worth considering a reduction of feed and fluid volume.

M's paediatrician identified that increasing feed intolerance, distress and peripheral oedema were poor prognostic indictors. Discussions were held with M's family who reiterated their desire to focus on M's comfort and to care for her at home. She was discharged home with increased nursing support in the home. A symptom management plan was in place with low dose morphine and buccal midazolam as pharmacological management of periods of distress.

Over the coming weeks, M's feed tolerance continued to deteriorate, feed volumes were gradually reduced. Her paediatrician, GP and homecare nursing team remained closely involved in her care. After 3 weeks at home she was no longer able to tolerate any enteral feed, experiencing distress with minimal amounts. She was very sleepy and no longer able to tolerate any time in her chair.

All feeds and enteral medications were discontinued and M was commenced on continuous SC infusion of morphine, midazolam and glycoopyrronium bromide. She remained comfortable and died at home surrounded by her family 5 days later.

Feeding intolerance and peripheral oedema are indicators of intestinal failure and poor prognostic indicators in children with SNI . It is ethical to withhold feeds and fluids at end-of-life if continuing fluids is associated with increased symptoms and if it felt that a child is close to death, The Royal College of Paediatrics and Child Health have developed a useful framework which supports decision making in complex cases . Subcutaneous infusions can be used safely in a home environment and may help to achieve symptom control if a child can no longer absorb medications enterally. It should only be used when it is no longer possible to use oral or PEG tube route.

Conclusion:

These cases were chosen as they illustrate some of the common symptoms and challenges experienced in caring for children at EOL. Further discussion on these and other symptoms will be

held during the presentation and the audience will be encouraged to engage in the discussion and to calculate drug doses.

Useful resources:

The Association for Paediatric Palliative Medicine has developed a formulary of drugs used in children's palliative care. It is available for free from https://www.togetherforshortlives.org.uk/resource/appm-master-formulary-2017-4th-edition/

Other valuable resources include the Basic Symptom Control in Paediatric Palliative Care guidlelines available from https://www.togetherforshortlives.org.uk/resource/basic-symptom-control-paediatric-palliative-care/ and the WHO guidelines on persistent pain in children available from https://www.who.int/medicines/areas/quality_safety/guide_perspainchild/en/.

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Meet the Expert 3 - The crying infant: Assessment and management
Liffey Hall 2

Shalom Ben-Shimol, MD

Definitions

Crying is a normal physiological behaviour in young infants.
Physiologically, the peak of crying in infants is at 6 - 8 weeks of age, with babies crying on average 2 - 3 per 24 hours, after which it gradually decreases by the age of 3 to 4 months.

Excessive crying is usually defined as crying >3 hours/day for >3 days/week. This is often referred to as "colic".

Commonly used definition is Wessel's 'Rule of Three':

1. Crying that lasts for more than 3 hours per day,
2. Occurs on more than 3 days per week
3. Persists for more than 3 weeks

Episodes of inconsolable crying typically tend to cluster during the evening, but may occur throughout the day.

However, many babies present with lesser amounts of crying, as the parents perceive it as excessive.

Some studies defined "degrees" of crying [**1**]:

- Contented – no / minimal paroxysms of crying
- Fussy – otherwise healthy; excessive crying is defined as crying >3 hours/day for >3 days/week.
- Seriously fussy – >3 weeks or requiring medications

In the medical literature, the definitions of excessive crying are variable, and include [**2, 3**]:

- Differences in the number of hours of crying / day: usually >3, but also >4 hours
- Differences in the number of days of crying

- Differences in the number of weeks of crying (from 1 week to 3 weeks, usually)
- Subjective parental report - Inconsolable / problematic / crying a lot
- Differences in the age groups; usually, birth to 3, 4 or 5 months

Epidemiology (How common is common?)

Differences in the definitions of excessive crying result in different estimations of prevalence, and may lead to the inclusion of very dissimilar groups of infants [**2, 3**]. These estimations range from 1% to 40%, usually 10%-20%.

The cause of 10% to 20% of all early pediatrician visits of infants aged 2 weeks to 3 months. Underlying organic cause is found in less than 5% of these infants [**4**].

Etiology (the good stuff)

Infants with colic are well and thriving. There is usually no identifiable medical problem.
The parents are often distressed, exhausted, and confused, having received conflicting advice from various health professionals and lay sources.

An organic cause is revealed in only 5% of infants, with Urinary tract infections being the most prevalent (more than 50% of cases), especially in newborns [**5**].

Although the majority of cases are attributed to normal infant behavior, the differential diagnosis remains broad [**6**].

In most cases, the diagnosis can be set after taking a detailed medical history and performing a thorough clinical examination of the child.

<u>Common symptoms</u>

- Abdominal bloating
- Gas in abdomen
- Irritability
- Constipation
- Loose stool

<u>Possible common causes (1)</u>

- Hungry / thirsty
- Too hot / too cold
- In pain
- Over-tired
- Startled

<u>Possible common causes (2)</u>

- Gastro-esophageal reflux

- Gas producing food
- Air intake
- Milk allergy
- Allergic reaction

Red flags

- Fever
- Diarrhea
- Vomiting
- Eczema
- Failure to thrive
- Feeding difficulties
- Sandifer's positioning
- GI bleeding
- Red tympanic membrane – may be caused by excessive crying – but this is not enough to diagnose otitis media.

Etiology (the bad stuff)

Differential Diagnosis in the Pediatric Emergency Department includes [**7, 8**]:

- Skin: Hair tourniquet syndrome, diaper dermatitis, atopic dermatitis, rash, insect bites, and cellulitis
- Eyes: Corneal abrasion, glaucoma, conjunctivitis, and foreign body
- Ears and oropharynx: Acute otitis media or externa, stomatitis, aphthae, pharyngitis, and infant teething
- Cardiovascular system: Congenital cardiovascular anomalies, paroxysmal supraventricular tachycardia, and myocarditis
- Respiratory system: Nasal obstruction, bronchiolitis, laryngitis, bronchitis/asthma, pneumonia, and pneumothorax
- Gastrointestinal system: Volvulus, intussusception, appendicitis, hernia, gastroesophageal reflux, food allergy, acute gastroenteritis, lactose intolerance, constipation, and anal fissures
- Genitourinary system: Urinary tract infections, ovarian torsion, acute scrotum, meatal ulcer, and balanoposthitis
- Neurological system: Meningitis, encephalitis, head trauma, and increased intracranial pressure
- Musculoskeletal system: Bone fracture, septic arthritis, osteomyelitis, and developmental hip dysplasia

Notably, while Infants with colic are usually (~95%) healthy, this may not be true in the setting of developing countries [**9**]. Thus, in the setting of developing populations, it is important to consider the possibility of relatively high rate of "non-colic" diagnoses in a crying infant, including urinary tract infection, otitis media, gastrointestinal malformations etc.

Management

In most cases, the diagnosis can be set after taking a detailed medical history and performing a thorough clinical examination of the child.

In cases with "red flags", the differential diagnosis should be broader.

- Thus, following a normal history and physical examination, it is suitable to reassure and educate the parents.
- In cases with gastrointestinal "red flags" (Sandifer, vomiting, diarrhea, constipation, failure to thrive, familial history of atopy, GI bleeding etc.), it may be suitable to refer the child to GI specialist. Changing the baby diet or GE reflux treatment should only be considered after simple measures of parent's reassurance, education etc. [**10**]

In cases where organic disease is suspected, evaluation should include urine-analysis, otoscopic examination and other tests, specific to the scenario. These may include (among others) [**8**]:

- History: review of systems, feeding, perinatal, vaccination, and family history
- Physical examination: vital signs, general description, pertinent findings
- Tests of blood, urine, and cerebrospinal fluid
- Imaging studies (including abdominal ultrasound)
- Stool occult blood testing
- ECG

Ensuring the availability of family support is essential in the discharge planning. Families should also perceive the empathy of the physician and feel reassured about their safe discharge home [**6**]. Education about crying in normal infants is associated with a reduction in pediatric emergency room visits for crying complaints [**11**].

Possible interventions:

- Manual therapy [**12**]
    - Touching
    - wrapping
    - Cuddling
    - kangaroo caring
    - Swinging
- Cranial osteopathy [**13**]
- Probiotics [**14**]
- Playing white noise [**15**]
- Administration of glucose
- Using of pacifiers

Otitis media (some thoughts about my favorite red herring…)

Red tympanic membrane – may be caused by excessive crying – but this is not enough to diagnose otitis media. Nevertheless, assessment of otitis media is an important part of the crying infant management.
In different settings, up to 15-20% of episodes were associated with otitis media.

Large cohort study finds a statistically significant association between excessive crying in early infancy and subsequent ear symptoms [**16**].

Prevention of the first episode of otitis media (through vaccination with PCV) resulted in prevention of recurrent otitis media and complex otitis media [**17, 18**].

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Meet the Expert 4 - Expanding Newborn Screening – The Endless Possibilities

Liffey Hall 1

G.F. Hoffmann
University Children's Hospital, Heidelberg, Germany

Over the last two decades improved knowledge of rare diseases including "new" therapies and technical platforms, especially high-throughput methods for multicomponent analyses, have transformed newborn population screening. From 1995 tandem mass spectrometry expanded newborn screening programs have been developed in the USA, Europe and Australia. They became the most successful preventive approach in medicine. In parallel the detection, treatment and possibly prevention of individually rare genetic diseases have become one of the major challenges and focus in developed countries. A child with a severe handicap because of a late diagnosed metabolic disorder in Germany spends 40 - 60.000 Euros every year of life for direct health care costs only. The overall frequency of all disorders detected by the extended newborn screening program in Germany is now one affected baby out of every 1.000 newborns. The cost relationship for direct health costs in Germany is one million Euro invested in newborn screening against savings of > 70 million Euro of avoided direct health care costs. Comparison of extended screening programs in different parts of the Western world suggests that the incidences are universally ≥ 1:1000 in modern populations with a mixed gene pool and a low rate of consanguinity. The incidence rate increases rapidly in countries with traditional societies, especially influenced by the rate of consanguinity, e.g. to ≈ 1: 800 in Turkey and ≈1: 400 in Qatar.

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By 2019 > 20 European countries, the USA, Australia, Canadian provinces as well as Qatar and China have implemented expanded newborn screening programs, and more are considering expansion. In spite of the wide variety of screening panels adopted in the EU Countries, there is a remarkable uniformity in the approaches used to make decisions. The initial steps of newborn screening have a very similar timing across countries, whereas confirmatory investigations and treatments start rather late in some countries, compared with other countries. Quality control and quality assurance schemes are applied satisfactorily at the laboratory test stage, whereas subsequent steps of the process draw lesser attention. Their performance relies essentially on general quality control systems operated locally. The fraction of symptomatic cases at start of treatment is unfortunately rather significant for some diseases. As another problematic fact the number of disorders screened for by MS/MS ranges from eight disorders in Irland, 16 in Germany (17 from summer 2019 with the inclusion of SCID) to > 20 in others (up to 60 in the USA). The number of live births investigated per screening center varies from 18,000 to 200,000. Few programs have reported the number of positively identified cases and technical data, although many participate in quality assurance and proficiency test schemes. This does not reflect major differences in the genetic background of populations or estimated prevalences, but rather highlights different approaches to the estimation of risks and benefits and just lack of evidence. Detailed knowledge about the natural course of many diseases and their variants, information on middle- and long-term outcome after early treatment initiation are still insufficient.

There are several ongoing studies evaluating the implementation of further improved analytical methods including primary genetic testing into newborn screening programs. For example, 26 additional target disorders (25 genetic metabolic disorders and vitamin B_{12}-deficiency) are currently evaluated in a prospective study at the Newborn Screening Centre Heidelberg, Germany, using second-tier strategies for 15 of the additional metabolic target disorders. From August 2016 - December 2018 190,589 children participated in the study. Second-tier analyses were performed in 7% of samples. The recall rate was 0.1% for the additional target disorders. Target disorders from the study panel were confirmed in 58 children: 1 HMG-CoA-lyase deficiency, 1 citrullinaemia type I, 3 MAD deficiency, 2 MTHFR deficiency, 2 propionic aciduria, 5 OTC deficiency, 1 carnitine transporter deficiency, 1 tyrosinaemia type I, 1 maleylacetoacetate isomerase deficiency, and 42 children with maternal vitamin B_{12}-deficiency (1 with MAD deficiency + vitamin B12 deficiency). All

mothers of children with vitamin B_{12} deficiency were offered standardized work-up for vitamin B_{12} deficiency and were referred to internal medicine for further diagnostics and treatment if indicated. At diagnosis 52 patients were asymptomatic, 6 symptomatic (5 OTC deficiency, 1 severe MAD deficiency). Three of 6 children diagnosed symptomatically deceased despite early treatment (2 OTC deficiency, 1 severe MAD deficiency).

Next generation sequencing has opened an entirely new perspective of diagnosing genetic disorders. Unprecedented methodology enables novel approaches to identify pathogenic variants at the genomic level and to make predictions on their effects on disease risks leading into an era of genetic-guided medicine, most notably “personalized” and “precision” medicine. In parallel, the first really successful therapies for specific genetic diseases in childhood have appeared and many more are being developed, e.g. spinal muscular atrophy, aromatic L- amino acid decarboxylase deficiency, etc.. Again the principal paradigm remains that only after early detection the disease course can be changed from devastating impairment and early death to normal or close to normal development. Technology and costs (< 100 € per sample for a targeted exome) would allow successful integration of these “new” diseases by next generation sequencing into newborn screening programs. However, these techniques need to be customized for the newborn screening concept and carefully evaluated in real life operation. Especially the natural history and the spectrum of diseases are often not well enough defined, even in “old” diseases, such as Werdnig-Hoffmann disease – SMA. The first pilot projects have started.

After decades of slow developments and being able to concentrate on program optimisation and improving quality schemes, newborn screening is now being rapidly transformed by new technologies, therapies and expectations. Harmonisation of disease screening panels, spectrum of metabolites analysed, sizes of screening laboratories, analytical procedures, and proficiency and quality testing are all urgently warranted on the European level (and beyond). The huge difference of recall rates illustrates one obvious and important area for improvement. There is a need for universal metrics to allow interlaboratory comparisons, quality assurance schemes, approved training schemes for provider competence in interpretation, as well as interlaboratory cooperation in second-tier strategies (e.g. possibly one specialized second-tier test in one laboratory only). An important issue is the development and evaluation of uniform follow-up and confirmatory testing of patients leading to uniform guidelines. The long-term benefit of all programs has to be evaluated

thoroughly which for most of these rare diseases can only be achieved through close and coordinated international collaboration on long-term follow-up and outcome. By now these challenges appear more complex than technological hurdles. Finally, following high-throughput methods for multicomponent biochemical analyses high-throughput methods for molecular analyses are now ready to be implemented into newborn screening programs with the old as well as a whole array of new challenges and possibilities. Paediatrics should remain in the driving seat – for the benefit of patients and society.

In-Depth Readings

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