SCN2A Europe

Autism, Epilepsy and Genetics
An experience with the gene SCN2A

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Summary

Autism, intellectual disability and epilepsy significantly impact our society, for different reasons. Recent research shows SCN2A is playing an important role in diagnosis of these presentations – Mutations in the gene SCN2A bring at least one of these disorders and often all three.

Researchers predict (annually) 7000 newborns worldwide will carry a SCN2A mutation. Estimating more than 500.000 people are currently affected and the vast majority are undiagnosed.

Epilepsy in infancy will often trigger a genetic testing; however, this is uncommon for late onset epilepsy, autism and/or intellectual disability. Available medical interventions differ depending on the specific SCN2A mutation and, therefore, it is imperative to receive a correct diagnosis and to diagnose as many carriers of a SNC2A mutation as possible.

This poster would like to show the current prevalence of SCN2A mutations and the importance of early genetic test, using the example of a real case.

Introduction

The impact of autism (ASD), intellectual disability (ID) and epilepsy in our society is significant – e.g. for children in the United States 1,2% ID[1]; 0,6% epilepsy[2]; 1,9% ASD[3].

Genetics play a relevant role in all three presentations, studies show. SCN2A mutations are becoming more and more relevant in the recent years, with these three phenotypes being the most observed in the SCN2A population.

Fig. 1. Percentage of US children with ASD, ID and epilepsy

Erik, 8 years old, was diagnosed with autism and intellectual disability at the age of 2 and with epilepsy at the age of 5.

Prevalence of SCN2A related disorders

Experts[4] consider that the number of SCN2A cases is similar to the *Dravet* syndrome. *Dravet* is better known by scientists and clinicians, and normally related to a SCN1A mutation. Previously, the prevalence of *Dravet* syndrome was between 1:20.000 and 1:40.000, current figures are now estimated at 1:10.000 to 1:15.000.

Such a prevalence for SCN2A related disorders would mean that, every year, 7.000 new born worldwide carry a SCN2A mutation, and that more than 500.000 people are currently affected in the world. However, due to lack of access to genetic testing, very few being diagnosed, probably less than 1%.

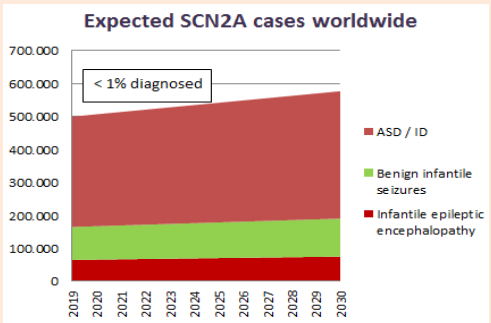

Fig. 2. Expected SCN2A cases worldwide until 2030

SCN2A is not diagnosed as frequently as *Dravet* syndrome because of its differing presentations: SCN2A mutations can express in a number of different ways, depending on how 'excited' the sodium channel is - the most common:

- If the sodium channel is overexcited (i.e. there is a Gain-of-Function GoF), epilepsy will be the main issue, usually within the first month of life.
- If the sodium channel is not excited enough (Loss-of-Function LoF), ID and ASD will be the presentation; however, epilepsy can present later in life.

Erik first presented with autism and intellectual disability and has a Loss-of-Function (LoF) in his genes.

Different medication for different function

Gain-of-Function (GoF) cases are characterized by early onset of catastrophic seizures. Due to the nature of the seizures, neurologists are involved early and these cases are often forwarded for genetic testing. On the other hand, Loss-of-Function (LoF) cases are characterized by ASD/ID; seizures may (or not) appear later – clinicians dealing with autism have less access to genetic testing; if seizures are mild or do not present, then often no genetic testing will be ordered.

To know whether the SCN2A mutation brings a Gain- or a Loss-of-Function is crucial – otherwise, you risk giving the wrong antiepileptic drug: e.g. so-called sodium-channel-blockers are normally avoided in Loss-of-Function cases.

Erik, who is a Loss-of-Function case, received > 1 year long sodium-channel-blockers, showing no real improvement.

Importance of genetic testing

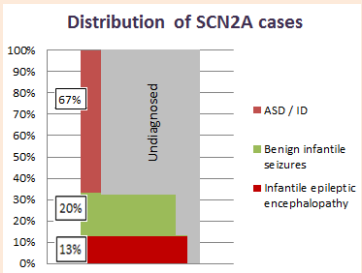

Fig. 3. Distribution of SCN2A cases: 1/3 show early onset epilepsy, 2/3 show ASD/ID (~20% diagnosed)

Erik was diagnosed with a SCN2A mutation at age of 5.

Only through genetic testing it is possible to identify SCN2A cases. Among the SCN2A cases, around 1/3 have epilepsy as the main issue (although an important part reveal as benign infantile seizures, which disappear at the age of 2) and 2/3 have ID/ASD as main issues.

Genetic testing will most likely be offered by neurologists who identify epilepsy, but what about Loss-of-Function cases without or just mild epilepsy? Genetic testing needs to be offered also in this particular group.

Conclusion

It is imperative that all presentations, whether LoF or GoF, of SCN2A receive genetic testing to ensure the correct medication can be prescribed. Increased diagnosis will also lead to further research and potential treatments for all presentations of SCN2A.

Further genetic testing needs to be accessible and promoted, especially among ASD/ID clinical experts. In the absence of epilepsy, other comorbidities can be used to increase the likeliness of identifying SCN2A cases.

References

[1]Centers for Disease Control and Prevention, NCHS Data Brief No. 291, November 2017, Fig. 3
[2]Centers for Disease Control and Prevention, Epilepsy Fast Facts
[3]Centers for Disease Control and Prevention, Surveillance Summaries / March 27, 2020 / 69(4);1–12
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