Providing rare disease patients with the support they deserve

Bojana Mirosavljevic, PhD, Patient Engagement Officer at Ergomed/PSR Orphan Experts, recounts how the loss of her daughter to a severe form of Batten disease, and her experience overcoming the challenges of rare disease diagnosis in Serbia, still drives her work to put the patient at the centre of rare disease research

Can you take us through your daughter Zoya's illness and when her symptoms began? She was originally diagnosed with epilepsy; how did you know this wasn't the right diagnosis?

Zoya was born on 24 September 2004 as a completely healthy and wanted child. The whole world was ours and every day we enjoyed our beautiful little girl who was developing completely normally.

A few months after she turned three, Zoya had her first epileptic seizure. Of course, we were in a complete panic. We had never seen a live epileptic seizure before and we knew nothing about it.

Although the doctors kept convincing us that it was "ordinary epilepsy" and that "people with epilepsy live normally today", over time we noticed that Zoya was losing her balance. That was our first sign that it was not ordinary epilepsy, but something more serious. However, even then, the doctors did not take us seriously, but told me that I was "just another panicked mother", whatever that meant.

Soon after, Zoya literally stopped walking completely in one day, stopped talking and lost even her sight – she didn't even recognise us. She was so scared then because she didn't know what was happening to her, and we couldn't help her. The feeling that completely destroyed us was

that we could not help her in any way, and it is the obligation of the parent to help the child, right? Our little girl was disappearing day after day before our eyes, and there was nothing we could do. That helplessness was killing us.

How did she eventually come to be diagnosed with Batten disease, and what difficulties did you encounter in reaching that diagnosis and in trying to access treatment?

When Zoya suddenly lost all her functions, the doctors at the children's hospital in our city told us: "Well, you were right after all, it's something serious. Now, Zoya will decline during the next years, and we will figure out what exactly is wrong with her based on how she declines."

Of course, this is not acceptable for any normal parent and we took Zoya to the Belgrade Institute for Mother and Child at our own cost, where they did all the possible analyses that were available in Serbia at that time. And very honestly, the doctors of that hospital said that Zoya had a rare disease and that she had to go for diagnostics abroad where such tests are available. They sent some documentation off for government health insurance, but they refused to send Zoya abroad for diagnostics, even though the doctors had recommended it.

At that point, Zoya had had over 200 epileptic seizures and we didn't have the time or resources at the time to fight such a scandalous decision. We urgently sold everything we had and borrowed money from a friend to go to London at Great Ormond Street Hospital on our own arrangements. The journey was very difficult due to Zoya's frequent epic seizures on the airplane, and

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we were left to ourselves, without any support from doctors or the government.

At the London hospital, they quickly diagnosed Batten disease with no doubt; they just took Zoya's blood and our blood and cancelled all the tests we had because they were completely sure of the diagnosis of Batten disease. They had seen children with the condition many times before.

Then we returned to Serbia with that horrible diagnosis, about which no one knew anything and no one had heard of.

Zoya very soon afterwards needed to be tube-fed. She had gone from being a completely healthy child, to one unable to walk, and she needed all 24 hours of our care.

You were eventually successful in getting 'Zoya's Law' passed in Serbia. How did you and your family achieve this, and what has been the impact of the law?

Zoya lost her battle in August 2013. She passed away one month before her ninth birthday. We were completely broken – time stopped. That period was really very difficult.

We knew we had to find a reason to breathe again or we were done. Our only goal was to prevent anyone from going through the sadness and pain we go through every day.

As soon as we got back from London, we sued the government over the health insurance and won the process; we were the first family in Serbia to win a lawsuit over health insurance. That victory was the basis for Zoya's Law. The fight for Zoya's Law was very hard and difficult for our broken hearts. We knew it was the right thing to do and we had to do it, both for Zoya and for us. For us as a family, it was very hard to expose our pain and sorrow like that, but we had a higher goal – everyone has the right to a diagnosis and everyone deserves a chance to fight.

Zoya's Law now makes it possible to diagnose rare and genetic conditions in Serbia. It has four parts: pre-natal diagnosis; pre-implantation genetic diagnosis; the mapping of pathological genes within affected families; and the sending of samples to a global reference laboratory if a diagnosis cannot be made nationally.

Zoya's Law was passed unanimously in January 2015. It is the only law to have ever been adopted unanimously in Serbian parliament. Since then, it has saved more than 3,000 lives. I presented Zoya's Law in the European Parliament in Brussels, and at the United Nations in New York, as well as at more than 80 conferences all over the world, winning numerous awards.

I want to believe in a reality where everyone has the right to a chance to fight for life. Getting a diagnosis must not depend on someone's goodwill or the country in which they lives. It is a basic human right and it would be good if every country had Zoya's Law.

Based on your own journey, how do you think the path to diagnosis can still be improved for rare disease patients?

There are still large differences in diagnosis from country to country; that is unacceptable. Life must not depend on geography. When it comes to rare diseases, for instance, the length of time from symptom onset to an accurate diagnosis is on average four to seven years, depending on the country where the patient lives. When I say average, I refer to the fact that, unfortunately, there are far less of those whose time to an accurate diagnosis is less than five years, and there are more of those where it takes more than seven years. For example, in our association, we have a member who, after 15 years, managed to get an accurate diagnosis of a rare disease. This is too long.

I think the problem is that in each country there is a different rule regarding the right to a diagnosis. There must be a law that obliges the doctor to deal with this. Let's be clear: there will always be diseases that cannot be diagnosed, because, for example, they are completely new. This is supported by the fact that five new rare diseases are discovered every week. But the doctor has to try to reach a diagnosis and can't just write off the patient because he can't make one accurately.

We know that there are over 7,000 rare diseases and one cannot expect one doctor to know all of them. That is not realistic, but if someone doesn't know something, they should have to send the patient somewhere and to someone who knows more.

Why are clinical trials so important for rare disease patients?

On the journey to the diagnosis, the average rare disease patient changes specialist doctors between five and eight times, and during that time receives between three and five wrong diagnoses. More than 75% of patients with rare diseases are children, and 30% of patients die before their fifth birthday.

I must mention that these are numbers and statistics, and of course we all need them, but these numbers take on a completely different dimension and meaning when your child is or when you are part of them. Time is crucial for people suffering from rare diseases. Sometimes it takes 15 years for a drug to reach the market and become available to patients. Patients with rare diseases cannot wait for that.

In December 2018, Bojana Mirosavljević was the recipient of the EURORDIS 'Written Media Award 2019' in recognition of her specialised journal for rare diseases *Word for Life*

It is known that less than 5% of rare diseases have a therapy, which means that over 95% of rare diseases do not have a therapy. The only option for these patients is a clinical trial. That is their only chance.

I am committed to raising awareness of the importance of clinical research among patients, but also among physicians. Doctors do not know enough about the process of clinical research and I think it is important to pay extra attention to this problem.

Why is it important to take a patient-centric approach when it comes to designing clinical trials, especially for rare disease patients? How else can a patient-centric outlook help?

When we speak about the importance of clinical trials in rare disease, the importance of patient-centricity is even greater. Very often there are no guidelines on what the most appropriate endpoints are or what outcome measures could be used for those diseases which are extremely rare, some of which don't even have a name. The patient is a key stakeholder: the bridge between all other stakeholders.

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Patients can give information and insight about the impact of their condition and treatments on their daily lives that are not available elsewhere. They are in a unique position to describe the outcomes that matter to them and to inform about the potential positive or negative effects of new and existing technologies on their health and on their ability to live and work.

Patients bring to the table their unique lived experience of specific conditions and of their care and medication, and are motivated to engage. There is an increasing need to draw on patient knowledge and experience in order to understand what it is like to live with a specific condition, how care is administered, and the day-to-day use of medicines. This input helps to improve discovery, development, and the evaluation of new, effective medicines.

Patient advocacy groups are driven to participate in research because the disease has affected them or someone they know. Patient organisations can help to plan, guide and coordinate patient involvement, which can then help researchers approach their work from a new perspective. Include patients in the design and management stages, and that guarantees that ethical and safety issues are covered from the patient's perspective.

Patients can and should be involved in all phases of drug development, ranging from drug discovery until registration and post-approval activities. To ensure high levels of engagement, patient-centricity should be continuous throughout all phases of research.

What continues to drive your conviction to help rare disease patients, and why is Ergomed the ideal vehicle to achieve this?

My Zoya is my strength and my guide. She was so young, and she did such great things.

Patient-centricity has been at the heart of Ergomed's approach since the beginning. They really value the patient's input. They are not only in contact with patient organisations, not only involved in clinical trial recruitment, but they are there at an early stage to include the patient before finalising protocol, to get informed consent etc. We really want to have the conversation with patients about outcome measures and assessments. That's what makes Ergomed special: they not only listen to the patient's voice, but they also hear it. It's a concrete commitment to the patient.

Orphan drug development is Ergomed's core strength, and we are committed to improving the lives of rare disease patients and their families.

To find out more about Ergomed, please visit **www.Ergomedplc.com** or write to us: **info@ergomedplc.com**

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Bojana Mirosavljević is Patient Engagement Officer at PSR Orphan Experts/ Ergomed. Educated as a chemist and embryologist, in 2010 Bojana founded and is still president of Zivot-Life, an association for children with rare diseases in Serbia. She was also Founder and Chief Editor of the first and only journal about rare diseases in the Balkan region, and in 2017 established the first rare disease database in the Balkans. She is also known for spearheading the creation of new legislation, named Zoya's Law after her late daughter, concerning the prevention and diagnosis of genetic and rare diseases.