International Journal of Celiac Disease, 2019, Vol. 7, No. 2, 58-62
Available online at http://pubs.sciepub.com/ijcd/7/2/2
Published by Science and Education Publishing
DOI:10.12691/ijcd-7-2-2

A Dialogue with Professor András Arató

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Received April 04, 2019; Revised May 07, 2019; Accepted August 13, 2019

Abstract Here we are continuing interview articles and Professor András Arató from First Department of Paediatrics of the Semmelweis University in Budapest in Hungary is questioned.

Keywords: *interview, journal questions, a great personality*

Cite This Article: Gabriel Samasca, "A Dialogue with Professor András Arató." *International Journal of Celiac Disease*, vol. 7, no. 2 (2019): 58-62. doi: 10.12691/ijcd-7-2-2.

1. Would you be so kind and could you please shortly introduce yourself to the readers? Where are you born? Some information about your education and eventually some interest from this period?

I was born in Budapest, in 1953, as only child of my parents. That period was quite a difficult time in Hungary, as it was an overt communist dictatorship that time. Three years later broke out the revolution against this system, which was repressed by the Sovet intervention. I was that time only almost 4 years old, however I can recall some pictures which burned to my brain forever, such as the living in the cellar of our building or the tanks on the Andrássy Avenue.

My parents always valued very much the learning and the knowledge and I liked to ask them about the miracles of the nature and history. I enjoyed the school, learning was also an entertainment for me, and my parents appreciated very much my good results at school. I was interested especially in mathematics, but I liked other subjects, too. I enjoyed reading, first fairy tales, but very soon I read with great interest the Indian novels of James Cooper and the Adventures of Tom Sawyer and Huckleberry Finn from Mark Twain. One of my favorite book in this period was Heart from Edmondo de Amicis. I have to admit that although I was an excellent pupil in learning, I made quite a lot of mischiefs in the school.

After the elementary school I went to the Kölcsey Ferenc secondary school, where that time was quite a free atmosphere which was really enjoyable. I learned also Latin in this school, and I was very interested in ancient history and mithology, but at the same time I also enjoyed learning biology, chemistry and mathemathics. After passing my final examination I applied to the Semmelweis University and I was accepted. During the basic training my favourite subjects were biochemistry and physiology. It was great experience to start the clinical disciplines and meet the patients and learn the diagnostic process and how to make a good differential diagnosis. First I planned to be an internist, but during my practice in pediatrics I changed my mind and chose this beautiful field of medicine.

2. Where are you work and on what position? Some information about your daily routine job description?

I have been working at the first Department of Paediatrics, Semmelweis University since my graduation in 1977. I was appointed to a full professor in 2005 and I am the general vice chairman of this Department.

I arrive to work before 7 a.m. and I look around the whole department for getting information what happened during the night, especially at our Intensive Care Unit and Neonatal Intensive Centrum. At 8.00 I participate at the short talk of the management including the head of the department, the chief nurse to talk about the events of the last 24 hours and the tasks for the present day. At 8.15 starts our daily conference for the whole medical staff and residents, which is directed by the head of the department or by me in his abscence. This conference lasts for about 30 minutes and during this time every day usually a resident will give a short summary about a recent interesting paper published in the leading papers of pediatrics or in its subdisciplines.

At 9.30 I participate or lead the visit which take place at least once a week every wards and three times at ICU and NIC. Of course we will go out of turn to those patients where an urgent decision is necessary. After the conclusion of the visit I have to arrange special actual administrative tasks for the Department. Almost every day I have to examine some outpatient children, but on every Friday I have long consulting hours.

I teach pediatrics, pediatric gastroenterology to Hungarian and English speaking students regularly, I give seminars and practical training for them. I participate also in the postgradual training teaching residents in paediatrics and fellows in pediatric gastroenterology

I direct the research work of medical and PhD students in the field of pathogenesis of coeliac disease and inflammatory bowel disease. I also direct the work of Students' Scientific Association at our department. Every day I discuss with medical students, residents and PhD students come to me with their questions and I consult with them.

3. When you came directly contact with celiac disease?

I heard about coeliac disease only superficially during my gradual training. In the seventies this entity was not so well known in our country. After coming to the First Department of Paediatrics I was very eager to get know everything about paediatrics and look for those field where I could have started some research work, too. At last I noticed that István Kósnai cared for many infants and toddlers with coeliac disease and the majority of them had very severe form of disorders, with atrophy, protuberant abdomen, slim extremities, and some patients were in life threatening condition. The explanation of this severe manifestation was the very early introduction of gluten containing food to the infants‘ diet. It was costumary that time to give wheat grits to the babies at 2 months. Together we took care for more than hundred coeliac patients and analysed their clinical characteristics. We proved that the earlier the gluten was introduced to the infants'diet the more severe was the clinical manifestation of coeliac disease.

Dr. Kósnai was the first in Hungary, who did small intestinal biopsy in 1976. He used the Crosby-Kugler capsule with two ports. The biopsy was taken blindly, but the location of the capsule was controlled under X-ray using contrast substance. We strived to reach the Ligamentum Treitz, but this had not always succeded. With these methods we were able to take proper specimens, which were easy to orientate. At the same time Istvan called my attention for professor John Walker-Smith‘ important book with the title: Diseases of the small intestine in childhood. I had learnt quite a lot from this work.

Dr. Kósnai was my first mentor who launched me in pediatric gastroenterology and also starting my first sicentific study. He also started very fruitful cooperation with the pediatric gastroenterological research team of University of Helsinki directed by Professor Erkki Savilahti. In 1986 I also had the opportunity to spend half a year, and then in 1989 and 1992 3-3 months at this research laboratory, where learned several immunohistochemical methods for the analysis of lymphocyte subsets in children with coeliac disease and ulcerative colitis. Erkki Savilahti was also my important mentor, I had learnt from him how to plan and realize a scientific study and how to evaluate the results. I was really very happy when my very first paper in English was accepted by Gut in 1987.

4. How would you assess the changes in celiac disease by looking at the past period up to now, what has changed and what not?

During the last four decades tremendous changes happened in the clinical presentation, as well as in the diagnostic possibilities of coeliac disease. As for the therapy, no changes happened, the gluten free diet stayed mandatory, but there are strivings to replace somehow this diet, but none of these modalities can replace the gluten-free diet. As I mentioned above, in the seventies coeliac disease had the classical form, frequntly with very severe manifestations. Nowadays we observe much milder symptoms, which sometimes make it very difficult to recognize coeliac disease. Therefore we have to think of this disease even at mild an uncertain symptoms, for instance at iron deficiency anemia, constipation or at short stature. It was also recognized during the last decades that coeliac disease can exist in silent form, with villous atrophy but without any obvious symptoms. This kind of manifestation occurs very frequently in those disorders which associates frequently with coeliac disease, as for example in type 1 diabetes mellitus, osteoporosis, dental enamel deficiency, ataxia, dermatitis herpetiformis Duhring or in epilepsy. Luckily we have very efficient serological methods for screening

Forty years ago we had to do three jejunal biopsy for proving the diagnosis of coeliac disease, as that time no reliable serological tests were available. In every children we had to start also gluten challenges, and it was the so called two years rule, which declared that if the jejunal mucosa will stay intact even after two years‘ gluten challenge, the coeliac disease could be excluded. Now we know that this was not true, as it can occur histological relapse even after two years' challenge. That time not even immunohistochemical methods were available for helping the diagnosis.

The quality of gluten free diet has been developed very much in the last two decades, we have a large choice of good quality products which help the patients to comply much better to the diet. This development can be explained that gluten free diet became quite trendy, as its beneficial role in the treatment of non-coeliac gluten sensitivity was recognized. Nowadays more and more people consume gluten free diet even without any real indication, in the United States about 10 percent of the population keeps gluten free diet.

5. What was the most progressive and most important moment in the research of celiac disease and what are future research steps in celiac disease field?

Arateus was the first, who described the typical clinical picture of coeliac disease two thousand years ago: “Emaciated and atrophied, pale, feeble and incapable of performing any of his accustomed works, but if he attempts to walk, the limbs fail, the veins in the temples

are prominent, for owing to wasting the temples are hollow." (translated by Paveley WF, BMJ 1988).

.For my opinion, during these long history the most important moment was when Willem Dicke discovered in 1950 that gluten is the trigger factor in coeliac disease. He noticed his hospitalized coeliac toddlers, who existed on "gruel" (porridge) in the food scarce days of WWII, improved when wheat flour was not available but rice or potato flour was used. When Swedish planes dropped bread in The Netherlands, his patients who had improved on wheat-free diets, all relapsed.

The last important step in the history of coeliac disease happened in 1997, when Walburga Dieterich recognized that in coeliac disease tissue transglutaminase is the autoantigen, and it is the substrate of antiendomysial, antireticulin and antijejunal antibodies. It was proved that coeliac disease is an autoimmune disorder. This is especially interesting, because this is the single autoimmune disorder, where we know the trigger factor, the gluten.

I think that the most important future steps will be the discovery of those environmental factors which are responsible for the development of coeliac disease in those persons, who have the characteristic MHC constellation. Presently we do not know what is the explanation that 25% of population have the relevant DQ2 and/or DQ8 antigens, however only 1-1,5% of the population will have coeliac disease. I think that the microbiota and microbial transglutaminase enzymes are important environmental factors responsible for the development of this disorder.

6. Would you be so kind and can you shortly describe the research results of your research group in the celiac disease field, eventually say something about your current research in the celiac disease field?

As I previously mentioned I became expertized in immunohistochemical studies in Finland. There we studied the HLA-DR expression by surface and crypt epithelium and the numbers of cells of natural killer (NK) phenotype and of IgE containing cells with monoclonal antisera using the peroxidase technique. In coeliac patients when on a gluten containing diet the crypt epithelium showed strong HLA-DR expression, while this was not observable in children on gluten free diet and in control. As compared with control specimens biopsy specimens from untreated coeliac patients showed smaller numbers of NK cells in the lamina propria. No difference was found in the numbers of IgE containing cells between the patients and controls. The strong expression of HLA-DR by the crypt epithelial cells in coeliac children on a normal diet suggest that these cells are involved in the presentation of the antigen.

The number of intraepithelial lymphocytes (where the CD8 cells predominated) were significantly raised in patients taking gluten. It was an interesting finding that 10 to 20% of the patients' intraepithelial CD3 T cells expressed neither CD8 nor CD4 surface antigens. We hypothesized, that these $CD3^+CD4^-CD8^-$ cells could be gamma/delta T-cells. We proved this in our consecutive study as we found that within the jejunal epithelium, the number of gamma/delta + cells was elevated before and during gluten elimination and after the challenge test. The absolute number of intraepithelial gamma/delta + cells remained constant during gluten elimination and provocation. We infered that the constantly elevated population of gamma/delta + T cells in the epithelium of celiac patients might play an important role in the pathogenesis of celiac disease. The permanent elevation of gamma/delta T-cells made it possible to diagnose coeliac disease even on a gluten free diet, when the diet was started before definitive diagnosis.

During the nineties of the last century, it was possible to introduce of the immunohistochemical methods in our research laboratory and gradually started to use molecular biological methods for studying the different mRNA and protein expressions in the small intestinal biopsy specimens in children with treated or untreated coeliac disease.

We started to examine the expression of toll like receptors in coeliac children on gluten containing or gluten free diet. This was important step because in the pathogenesis of coeliac disease not only adaptive immunity but the innate one also have a decisive role. The p31-p43 gliadin peptide does not bind to HLA-DQ2 or HLA-DQ8; therefore, it does not stimulate $CD4^+$ T cells. This peptide could be recognised by Toll-like receptors or other pattern-recognition receptors of intestinal macrophages and dendritic cells, leading to increased synthesis of interleukin (IL)-15.

We found higher TLR2 and TLR4 mRNA expression and protein levels in the duodenal mucosa of children with treated and untreated coeliac disease compared with controls. TLR2 and TLR4 mRNA expression and protein levels were even higher in the duodenal mucosa of children with treated coeliac children than in untreated ones. Our finding of elevated TLR2 and TLR4 expression even in treated patients with coeliac disease is congruent with our earlier finding of elevated numbers of intraepithalial gamma/delta T cells on gluten-free diet. It is well known that gamma/delta T cells have an important role in the innate immunity, and their activation is directed by TLRs.

The transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) was shown to exert protective effects in several immune-mediated disorders. Activation of PPARγ suppressed the expression of thymic stromal lymphopoietin (TSLP), an inducer of proinflammatory cytokines. Since the role of TSLP in gluten-sensitive enteropathy is completely unknown, we investigated the involvement of TSLP and its regulator PPARγ in childhood coeliac disease. Duodenal localization of PPARγ and TSLP was studied by immunohistochemistry.

In duodenal mucosa of children with coeliac disease, the amount of PPARγ was significantly lower and simultaneously that of TSLP significantly higher compared to controls. In patients on gluten free diet, the

levels of PPARγ mRNA and protein were significantly higher while that of TSLP markedly lower compared to newly diagnosed coeliac children. Immunohistochemistry revealed PPARγ and TSLP expression in lamina propria immune cells and in enterocytes.

Low expression of PPARγ and high expression of TSLP in the duodenal mucosa of children with newly diagnosed celiac children suggest that they are involved in the pathophysiology of coeliac disease. According to our result, it is very probable that PPARγ may be an inhibitory regulator of TSLP-stimulated inflammatory processes in coeliac patients.

We examined the prevalence of coeliac disease among 205 Hungarian children with T1DM, the frequency of coeliac disease was 8,3%. According to our results, the frequency of coeliac disease in Hungarian children with T1DM corresponds to the upper range of the published prevalence data in other countries. We published this result in 2003. In our further study it was found that in patients with T1DM, the CD14 C-260TT homozygous genotype increases the risk for the development of coeliac disease. The distribution of HLA-DQ genotype is different in children with coeliac disease and T1DM than in children with coeliac disease or T1DM only. Our results confirm that for coeliac disease the major susceptibility factor is DQ2, whereas for T1DM DQ8 is a stronger susceptibility factor than DQ2. The risk for development for both coeliac disease and T1DM is increased when DQ2/DQ8 heterozygosity is present. Determination of the HLA-DQ genotype in children with T1DM may help in estimating the risk for the development of coeliac disease.

It is more and more probable that T1DM is also gluten sensitive disease. Currently we plan to examine the intestinal permeability in children with both T1DM and coeliac disease and compared the values to those of patients with treated and untreated coeliac patients wothout T1DM, as well as to controls. We presume that in children with both T1DM and coeliac disease complying with a strict gluten-free diet the intestinal permeability is smaller than in patients only with T1DM. In vivo the intestinal permeability will be measured by with lactulose/mannitol (L/M). We plan to do this investigation in adult first degree relatives. We hypothyse that the intestinal permeability in first-degree relatives of T1DM patients with gluten free diet is decreased compared to those relatives who are on a normal diet.

7. Do you think there are differences in the concept of coeliac disease between some countries and especially what is the situation in Hungary in the celiac disease field?

The management of children with coeliac disease is standardized in Europe according to the present guideline by ESPGHAN published in 2012. Now it is not necessary in every for the diagnosis the analysis of intestinal biopsy speciemen. Diagnosis can be established without biopsy, if the patient has characteristic clinical symptoms, the anti-TTG titer is over ten times of the upper limit of normal, EMA test is positive and HLA-DQ2 and/or -DQ8 antigens can be detected. Every other situations it is necessary taking biopsy. The situation is a bit different in North-America, where always examine the biopsy specimens for the diagnosis.

In Hungary we comply with this ESPGHAN guideline, and in recent years in many cases we made the diagnosis without biopsy. In the majority of cases, the diagnosis is made by pediatric gastroenterologist.

Very soon it will be published a modified guidline about the diagnosis of coeliac disease by ESPGHAN and probably it will not be necessary the HLA analysis for the diagnosis of coeliac disease without biopsy.

In recent years, it is a troublesome problem, that many times the gluten free diet is introduced only on assumtion of coeliac disease without a correct diagnosis. This a very unpleasant situation, because it makes very difficult to prove or exclude the existence of coeliac disease.

In Hungary, we prescribe the patients a strict gluten free diet similarly to the other European countries and we check regularly the anti transglutminase titer for estimating the comliance to the diet.

8. Can you tell, what are the most frequent problems you meet in your pediatric practice in the management of coeliac children?

The most important problem is the introducing the gluten-free diat without diagnosis as I mentioned above. Quite frequently the parents browse the internet and following such sites which suggest the gluten free diet without mentioning the importance of previous clear diagnosis. In such a situation we suggest to the children and their parents to go back to the normal gluten containing diet and ask them to monitor the onse of any symptoms and we have to check the patient regularly observing the any clinical symptoms and measuring the anti TTG antibody titers.

In our country, children with autism spectrum disturbances start very frequently without diagnosis of coeliac disease a gluten free diet.

It is also a problem, that the children and their parents make mistakes unwittingly in the gluten free diet. Therefore, in those cases when the anti-TTG antibodies persist, it is important the exact analysis of the diet with the help of dietetician.

9. What questions have the parents of the children with coeliac disease before and after diagnosis?

Before the diagnosis the parents ask what could be the cause of the diverse symptoms, sometimes they did not get any information from the general practitioner that coeliac disease could be suspected in background of the

clinical picture. When I mention the possibility of coeliac disease the parents ask about the severity of this disorder and about treatment, but usually they do not ask about details at that time. After confirming the diagnosis the parents have many questions and almost all ask how long time it is necessary to comply with a gluten free diet and usually they are frightened when I clearly declare that according to our present knowledge a lifelong diet is mandatory. Then they ask about possible new therapeutical modalities, when I mention that presently we do not have any alternative therapy but it is possible that in the future something new therapy will be discovered. Many parents ask about the special details of the diet and they get very thorough answer.

The parents ask quite frequently about the late complication of coeliac disease. In my answer I always emphasize that with complying with a strict gluten free diet the complications are avoidable.

10. How do you think the situation in the celiac disease will change in the near and in the distant future?

I think that in the near future the diagnosis will be further simplified and the intestinal biopsy will be abandoned more frequently. Screening for coeliac diease in such disease groups where the occurance of this disorder is frequent, will be introduced. Recognizing earlier coeliac disease and introducing gluten free diet, the severe complications will be avoidable.

The choice of gluten free products will be further improve helping the coeliac children comlying easier to the gluten free diet.

I think that in the distant future it will be possible to prove coeliac disease from blood test even in those patient who started gluten free diet before the exact diagnosis using the tetramer method which make recognisable the effector lymphocytes against gliadin.

11. Do you think that celiac disease will be one day fully curable and patients will not need gluten-free diet?

I think that it is possible to change the innate and adaptive immunity such a way that it do not lead an excessive autoimmune process elicited by gliadin, when we will able to selectively change the activity of those lymphocytes which are directed against gliadin and transglutaminase.

I also can imagine that in the distant future the gluten free diet might be replaced by alternative therapy. I think that the vaccination against different gliadin epitopes may be the most successful therapeutical option in this respect.

12. I think that for readers will be interesting, what is yourfuture objectives?

I want to study with my coworker those factors in the intestinal mucosa, which might be responsible for the development of fibrotic processes in intestinal mucosa of disease with immunopathogenesis. We look for answer for that important qustions why fibrotic process is quite frequently occur in Crohn disease, but almost never in coeliac disease, however in both disorder Th1 immunoreaction has a central role in the pathogenesis.

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