Uvea

Dr. S. R. Rathinam FAMS, PhD.
Uveitis service,
Aravind Eye Care System,
Madurai.
Email: rathinam@aravind.org

It is a distinct honour to be invited to share the experiences of my journey with uveitis patients. In a way treating a patient with uveitis is like a journey on Unknown River, witnessing its unexpected twists and turns in the course of inflammation, rapid swirling of iatrogenic complications, and calming pools of inflammatory control. Patient walk with us with a hope of getting rid of the disease as well the drugs, still journey is most rewarding when they regain their quality of vision and quality of life. If at all I have achieved something in this challenging field, it is mainly because of the lessons I learnt from my teachers and our patients.

After completing the National Board exams and working in general ophthalmology for 3years, I was posted under Prof. Namperumalswamy to examine uveitis patients. In 1993 we started separate uveitis clinic. Dr. Robert Nozik stayed with us for 2 weeks and examined all the cases, it was like getting taught from Dronacharya of Uveitis (Figure 1). The first puzzle was, uveitis comprised of diseases of diverse etiologies including infectious and non infectious causes. Even though the patients came with same diagnosis, the course, complications, sequelae and prognosis varied from patient to patient. We needed a database to follow them. It was 1993, there was no computer, and we had our register with manual entry. However this register tremendously

Figure 1. Robert Nozik, Proctor foundation is listening to the case history of a uveitis patient at Madurai Aravind in 1993. We started Uveitis clinic during his visit to Aravind.

Eminent Ophthalmologist's Journey

helped us to understand the pattern of diagnosis that we see every month. The trend changes in the new patients were immediately picked up. It was this register that showed there is sudden surge of non granulomatous pan uveitis in 1993.

Epidemic Outbreak of uveitis!

In 1993, South Indian city, Madurai had an unusual high rain fall and flooding. Following the rains, the people of Madurai suffered from an outbreak of fever which was treated as seasonal fever by their physicians. Subsequently, several of those patients came to Aravind Eye Hospital with uveitis. An elaborate history revealed that they were mainly from the flooded parts of Madurai and they had suffered from fever. Ocular examination revealed non granulomatous pan uveitis with hypopyon, retinal vasculitis, membranous vitreous opacities and disc hyperemia. Uveitis literature was researched thoroughly and this unusual clinical picture was not described previously. Common causes of fever were ruled out with appropriate laboratory tests. By this time, raising our concern, we already had three hundred patients in six months. Several resource persons including private practitioners, Corporation medical officers and Social and Preventive Medicine faculty at Madurai Medical College were approached to know the endemic infectious diseases of Madurai. Surprisingly there was no information available at that point of time. Subsequently several microbiologists were consulted. In-depth discussions pointed out a possibility of leptospirosis. Scientists of Madurai Kamaraj University guided the author to approach Prof. Ratnam, a Veterinary surgeon, Tamil Nadu Veterinary college, Chennai, who had done his PhD on Leptospirosis in animals. Dawn was breaking over the horizon! The results confirmed the leptospiral etiology beyond any bias with very high positive titers in samples and negative results in the controls. This part of the work resulted in our first International Publication in American Journal of Ophthalmology in 1997, 4 years after the outbreak. The paper received one of the highest citations among all our publications (99 citations). This clinical research success motivated us to do several basic, epidemiological and diagnostic researches on ocular leptospirosis and they resulted in a number of publications in peer reviewed international journals.

"A pilot study to establish leptospiral etiology of Uveitis" was conducted and it was published in Journal of Medical Microbiology, with a cover picture. The study of etiopathogenesis was published in the prestigious international journal IOVS. Thus research publications from Aravind and text book chapters on leptospiral uveitis built up the literature on one of the regional ocular diseases, namely leptospiral uveitis. We established a Leptospirosis laboratory in Aravind Medical Research Foundation and Dr. V visited our lab in 4th floor to see the leptospires under the microscope (Figure 2).

Figure 2. Dr. V visits the leptospirosis laboratory.1999 Prof. VR Muthukaruppan is explaining.

Next Epidemic at our door step!

In 2010, nearly 200 hundred patients reported to our hospital over the year with history of fever, joint pain as well as blurring of vision.The joint pains were very severe and affected the mobility of the patients. This time, the predominant ocular sign was retinitis or neuroretinitis unlike the previous outbreak which was mainly non granulomatous pan uveitis. The serum and plasma samples were tested for several common infectious diseases including typhoid, leptospirosis, human immune deficiency virus, tuberculosis, chikungunya and syphilis in local laboratories. On receiving

a negative work up, the samples were sent to Reference lab (URMITE) in France where the samples were tested for Rickettsia and Bartonella. The results were negative. Additional virological work up was needed. Dr. Manmohan Parida PhD, Defense Research and Development Establishment (DRDE) was approached with the help of Dr Lalitha Prajna, Head of the department and professor of microbiology, Aravind Eye Hospital. The samples were sent to Gwalior. Serology for Chikungunya and Dengue were done by lateral flow assay. The tests results came negative. It appeared that we have again landed on a dead end.

Figure 3. Proctor foundation recognize Drs, M.Srinivasan, Dr. P. Namperumal samy and Dr.Rathinam as Proctor research fellows. 2000

We never thought West Nile Virus!

Further in-house IgM ELISA and antigen-capture ELISA were performed for WNV at the DRDE lab. To our surprise, serology was positive for WNV. West Nile was never suspected by us, as the clinical pictures described in ocular WNV in the literature was chorioretinitis. What we saw in our patients were primarily retinitis and neuroretinitis. Moreover, serology is not the final test as it can be a false positive due to cross reacting antigens.

But it was!

Hence we needed further evidence to talk about the etiology. Serum/ plasma samples were again tested by Real-time polymerase chain reaction (RT PCR) at DRDE. The PCR product was sent for nucleotide sequencing. The BLAST analysis of RT PCR

Figure 4. All India Uveitis conference 2001 Lead Faculty Dr. Nozik,Dr Narasing A Rao Dr Emmett Cunningham. Dr V with us.

amplicon confirmed West Nile Virus genogroup I lineage.

Aravind is privileged again:

This is the first Indian report on West Nile Virus retinitis in the eye and this part of the work was published in the International Journal of Infectious Diseases, Journal of Clinical Virology and in Ophthalmology. Because of its unique nature of clinical presentation in India, the pictures were chosen for the cover in the Ophthalmology journal.

III Children go blind- An endemic disease- Is it TB?

Several children from villages in the East coast of Tamil Nadu had come to the ophthalmologists

Figure 5. All India Uveitis conference 2006 Lead Faculty Dr Narasing A Rao

Figure 6 First five fellows trained in Uveitis clinic Madurai. Dr Manohar Babu, Dr. Venu Nadella, Dr. Yogish Kamath, Dr. BalaMurugan and Dr. Anguish Kawali.

for unique granulomas in the anterior chamber of their eye. This problem was prevalent for over 30 – 40 years. It was always suspected as tubercular uveitis, by the ophthalmologists, however there was no laboratory evidence for tuberculosis. In 1994, supported by the Indian Council of Medical Research, we did smear, culture and polymerase chain reaction tests for tuberculosis on these granulomas. The test results were negative. Besides, these children never improved after anti tubercular treatment.

We had our first uveitis camp!

A work plan was drafted to visit the coastal villages from where these children came. Dr. Natchiar, Prof. of ophthalmology, Aravind Eye Care System was kind enough to arrange a uveitis camp , the team included Dr Lalitha Prajna MD, Microbiologist, Dr. Shantha, MD epidemiologist and the author, the ophthalmologist. To our surprise, village Sellananthal had 41 children with same granulomatous eye disease. Detailed interviews were conducted with the family members. It was found that they developed itching and a mass lesion in one or both the eyes after taking bath in the village pond and some of them lost vision. Initially water samples were sent to King Institute at Chennai for analysis, the report only talked about the salt content! Examination of water under the microscope in our laboratory showed us how far pond water can be contaminated! Later these children were brought to the base hospital and biopsies of these granulomas were taken.

A parasite shines under the microscope!

Collaborating with Prof. Narsing A Rao, Los Angeles, USA, and Prof. Fritche A Thomas, USA, histopathological analysis of the granuloma demonstrated a possible trematode etiology. Trematodes are flat worms, transmitted by snails. However, this was again a dead end as histopathology can neither pin point the trematode nor the snail.

Research on Snails- At a Snail's Pace!

Ophthalmologist has absolutely no training in zoology, things started to move in snail's pace. We

began to read about trematodes and snails. After meeting the Zoology faculty of Madurai College and American college and Lady Doak College at Madurai, the author visited several villages and collected several snails for identification. Snails were sent to Zoological Survey of India, Kolkotta, for identification. In 2000, trematode isolation from the snails were learnt from the parasitologists of Sun yat sen University, China. However, there are thousands of snails on the land and thousands of flatworms. It appeared hopeless, we may never find out "the trematode" that causes the disease. Irrespective of all our efforts, we did not find out anything solid till 2014, but the children we treated never bothered about the cause, but they were interested to greet us.

Author took Dr Narsing Rao to the villages in 2006, the children who were initially treated in 1993-97 were adults and employed, and they came to see us with gifts and smiles.

By this period, molecular diagnostics became very popular; we thought this technique can narrow down the possibility. We were searching laboratories for collaborative research on molecular diagnostics.

Snails slide up to North eastern India to know their name!

Professor R. George Michael, North Eastern Hill University, (NEHU), Shillong, Meghalaya, India, visited Aravind for some other purpose and patiently listened to the challenges we faced. Following his introduction, we approached his colleague Professor Veena Tandon, from the same university who was actively working on parasite biodiversity, molecular taxonomy and phylogeny. After several discussions over phone we sent the specimen to Meghalaya from Tamil Nadu.With her expertise in the field, it was possible to resolve the puzzle that existed around our children's eye for nearly four decades.

Molecular diagnosis with Real-Time PCR, Cyber green Assay, Bi-directional sequencing and BLAST analysis were done on both the granuloma and the trematode larva obtained from the snails. Theses modern techniques identified and confirmed the cause as Procerovum varium (a trematode of the family Heterophyidae). This work was published in the prestigious Journal, Archives of Ophthalmology. This remarkable research helped the doctors avoid unnecessary anti tuberculosis treatment which can be detrimental to children. Lalan Kumar Arya who assisted the initial collaboration has now registered his PhD under the author to study Immunopathogenesis of this disease.

Global impact of this research:

The trematode eye disease is found also in Sri Lanka, Brazil and Egypt. Our research has an international implication, Indian literature will help to diagnose and treat the children in other countries also.

I entered Aravind with uncertainty whether I will do something useful. Aravind, teachers of Aravind and our patients taught me a lot. I was lucky to be trained by the founders of this great institute. Now Uveitis clinic has completed 20 years; We have conducted seven uveitis conferences and six research methodology workshops. We have conducted ICMR, DBT funded basic research programs and seven drug trials. We have 65 peer reviewed publications from this clinic, of them 25 publications have been cited more than 10 times, with total of 812 citations. 26 students have done their MS thesis in this clinic. We also have a student doing his PhD. I greatly acknowledge my teachers, colleagues, our patients, nursing staff and administrative staff at Aravind Eye Care System who were with me throughout the course of the studies.