Good morning, thank you for joining us in this presentation today on protocols for visual surveillance in craniosynostoses. My name is Ken Nischal, I’m Chief and Professor of Ophthalmology at Children’s Eye Center of UPMC at Children’s Hospital of Pittsburgh. You may wonder why you want to talk about or hear about craniosynostoses it’s such a rare condition. The fact is that there are things that we’ve learned having developed a protocol for the visual surveillance in craniosynostoses that we are able to take into other aspects and treatments in ophthalmology and I’d like to share that with you.

Let’s have a look at this first slide. You can see a child with what we call a cloverleaf abnormality, this is a severe craniosynostoses or multi-sutural synostoses that gives a child very shallow orbits and you can see how the eyes are protruding, there is chemosis and this child’s eyesight is at risk. You’ll see that the craniofacial surgeons have advanced their techniques to such an extent that the picture at the bottom right shows a child that looks pretty much normal, but if you look carefully the left eye is exotropic, and it’s exotropic because the child only has hand movements vision in that left eye and in the right eye 20/80 vision. So as our techniques in the craniofacial world have improved and we’ve gone from integrating the child into a normal environment and normal everyday social interaction now our attention turns to function. And really that’s what this talk is about.

Craniosynostoses for those of you who don’t know is the premature closure of one or more sutures in the skull. The suture here which I’m going to show you here that is the sagittal suture, that is the coronal suture which may be unicoronal or bicoronal and that’s the lambdoid suture.
Syndromic craniosynostoses are conditions where not only do you get a synostoses but you get other features affecting other parts of the body. The famous ones that we know about are Apert, Pfeiffer and Crouzon. In Apert you get a syndactyly so the hands and fingers are fused, in Pfeiffer syndrome you get an anomalous thumb, and in Crouzon syndrome you have hands that are completely normal but you have the synostoses that is normally bicoronal. All three are caused by a mutation in a gene called FGFR-2, that’s Fibroblast Growth Factor Receptor type 2. What’s interesting about this gene is normally when you get a mutation in a gene the protein product is reduced so the function is reduced. But in this gene mutation there is a gain of function mutation, in other words the receptor thinks that it’s switched on all the time so it creates more and more fibrous tissue. The result is premature closure of the sutures in the skull. I want you to remember that because that’s a very important consideration later on in the talk.

Saethre–Chotzen is a condition due to twist gene mutations and the twist gene is responsible for myogenesis. Well it’s not surprising then that these children often have ptosis. Craniofrontonasal dysplasia is an X-link dominant condition which we are not really going to talk about very much and uniconoronal synostosis, that’s just one suture being affected can be caused by mutations in FGFR-3. We’ll talk about that later.

Have a look at this picture. The child on your left has a sagittal synostoses and you can see that the head is long and narrow, that’s because when you have a synostoses the growth of the skull occurs parallel to that suture but not perpendicular to it. The picture on the right is a 3-D CT scan of a child
with bicoronal synostoses and here the child has a very wide head and a narrow head anteroposteriorly.

So here is the first question, why the visual surveillance? Well traditionally ophthalmologists have been asked to see these children because of the possibility of raised intracranial pressure and the idea was that if your suture stopped, well had closed early but the brain continued to grow then you would get a tight brain, craniocerebral disproportion. And for a long time it was thought that this, the pressure rise when this happens would give you papilledema and therefore you’d be able to help the craniofacial surgeons and the neurosurgeons work out when intervention was needed. I’m going to show you how creating a protocol has helped us workout how to better monitor these children and how craniocerebral disproportion actually is not a common cause for the raised intracranial pressure in these children.

So the first question was is there a problem with the visual – with visual loss in these children? And if you look at this pie chart it shows that in the best corrected eye vision was better than – sorry less than 20/40, worse than 20/40 in 40% of children. In other words these children went through all the operations that they do, the cranial vault expansions that at the end of the day in 40% the best seeing eye would see worse than 20/40. Not necessarily a great visual functional result. And this paper was published in the British Journal of Ophthalmology where we reviewed the visual outcomes and amblyogenic factors in craniosynostotic syndromes in 141 cases. What we found in addition to the traditional thing of worrying about an optic neuropathy because of raised pressure is that these children suffer from the same amblyogenic factors that children, normal children without
craniosynostoses suffer from but at a higher rate. So 70% had strabismus, so they could get strabismic amblyopia. Anisometropia occurred in 18% where there was more than one diopter of anisometropia. In the normal age matched control that number runs at 3%. And then astigmatism which can cause meridional amblyopia occurred in more than 40%, sorry in 40%. This in a normal population this number is about 2%. So you can see already that these children are at risk of visual loss not only from craniocerebral disproportion which as I said is a small percentage of the cause, but from amblyopia.

Here is a child with Saethre-Chotzen syndrome and while you can only see the eyes you can see that he has an esotropia and a ptosis. So he may have astigmatism, he may have strabismic amblyopia, bu the point is if we just worry about the raised intracranial pressure we are going to miss the commonest cause of visual loss in children which is amblyopia.

So let’s have a look at another way of recognizing visual pathway dysfunction. Now amblyopia is a visual pathway dysfunction, but optic neuropathy due to raised intracranial pressure can also cause visual pathway dysfunction. The way that I like to do this is to use visual evoked potentials. Now before you all switch off I’m not talking about sweep VEPs, I don’t like sweep VEPs, I like a flash VEP and a pattern VEP. Why? Because I’m not interested in the visual acuity, I’m interested in the integrity of the visual pathway. And when we looked at a number of cases, I think it was 114 cases of children with craniosynostoses we published this in the Journal of Plastics and Reconstructive Surgery, what we found was that the majority of children, that 60% had an abnormal visual evoke potential when you did their VEP. Now why is that? Part of it is because the landmarks externally
on the skull that you use with a VEP are not in the precise place where the brain should be because of the skull asymmetry. But what this tells us is this, that in all cases you need a baseline VEP to be able to monitor the effect of the craniosynostoses on the visual pathway. If you don’t have a baseline you can’t see a change. And if you can see a change you can’t take a one off VEP result because it’s going to likely be abnormal. So that’s a very important consideration.

So why does the visual loss occur? Well we talked about amblyopia, and we talked – I showed you a very nice picture of a very shallow orbit, and that gives rise to exposure keratopathy. I want to show you some pictures of that. Optic neuropathy is better considered as visual pathway dysfunction, any dysfunction from the eyeball to the occipital cortex. And that’s a much better way of looking at the visual dysfunction that these children can get.

What about their exposure keratopathy? Well it’s very interesting you know, I see a lot of exposure keratopathy in children, but this group of children get a very unusual response especially that group that have FGFR-2 mutations. And I couldn’t understand why until I realized that FGFR-2 has an isomer called KGFR, Keratocyte Growth Factor Receptor which sits in the cornea. Now while this is just speculation it does – it does explain why they get such a heat epithelial healing response to exposure keratopathy. So how do you deal with that? You need to think a lot about prophylactic lubrication and you need to think about a temporizing tarsorrhaphy before something more substantial is done like a mid face extraction to try and get rid of the shallow orbits.
Okay, let’s go back to the visual surveillance. Have a look at this paper that we published in the Archives of Ophthalmology in 2006. We looked at the correlation between visual acuity, optic disc appearance and pattern visual evoke potentials in syndromic craniosynostoses before and after cranial vault expansion, and guess what? We looked at 8 cases and 50% of cases showed no swelling of the optic disc. I want you to take a moment, no swelling of the optic disc despite raised intracranial pressure. And in one, only in one case did you see a decrease in the visual acuity. So what does that tell us? That tells us that looking at the optic nerves by themselves is not reliable and relying on visual acuity children is not reliable either.

Let’s go back a bit. This is a case report that we published in Pediatric Neurosurgery, what that shows is that despite sustained raised intracranial pressure there were no clinical signs including swollen optic discs in this child and it was only indicated by a deteriorating pattern reversal visual evoke potentials after cranial vault expansion. And what had happened in this child was that despite having the vault expansion the VEPs continued to deteriorate. So the child had another imaging, a newer imaging and was shown to have developed hydrocephalus. So here we have a child who has no clinical signs but the only sign is a visual evoke potential that’s deteriorating. And here is that child’s record. You’ll see that in the fundus photographs that there is an area of anomalous what looks like swelling but it remains consistent, it doesn’t get worse as you go down the VEP which is deteriorating. But as soon as they intervene with the shunt, that’s the black star, the VEP starts to improve. But the appearance of the optic nerve is unchanged. What’s more interesting is that the white star shows you the point at which they did the cranial vault expansion and you can see the continued deterioration.
So let’s go back, why should the optic nerve not swell? And remember the cases that I’m – we are talking about have been FGFR-2 mutation cases, that’s Apert, Pfeiffer, Crouzon. Well what we did was we looked at the expression of FGFR-2 and FGFR-3 in the normal human embryo orbit, and when you do that - brown by the way means it’s staining. FGFR-2 stains heavily in the skull, you can see in the orbital walls, but also stains in the optic nerve sheath and in extraocular muscle. FGFR-3 only stains in the bone. What does that mean? It means that in those cases where we found that there wasn’t any swelling in 50% of cases there was a possible FGFR-2 effect because of the mutation causing the optic nerve sheath to become more fibrous, in other words less elastic. You need elasticity in your optic nerve sheath and the lamina fibrosa to transmit raised intracranial pressure. FGFR-3 which is a uniconal synostosis never gets raised intracranial pressure or very rarely does, and when they do their optic nerves always swell. That’s really quite important. Now it’s speculation but it makes sense as to why the optic nerve sheath would not swell.

All right let’s go and take this a step further. This is a case that we published in Pediatric Neurosurgery. These children have maxillary facial hypoplasia so their airways are narrow. But the tissue, their adenoid tonsil tissue is normal. So you’ve got narrow airways with the same amount of soft tissue, which means that they have difficulty breathing. And because they have difficulty breathing at night sometimes they get sleep apnea. I want you to think about that for a minute. Which other adult that we deal with who gets sleep apnea and can get raised intracranial pressure? Well patients with Pickwickian syndrome who get sleep apnea are known to get raised intracranial pressure and papilledema. Now those are adults and you could understand why an adult would have
– that would happen to an adult because their peripheral vascular system is not robust, but why would that happen in a child?

Well it turns out that in these syndromic craniosynostoses there is often a congenital absence of intracranial venous sinuses. When you get this absence you get venous collaterals and the one thing collaterals don’t do, collaterals do not obey autoregulation. So what happens here we think is that these children get sleep apnea, the intracranial venous pressure goes up with the raised CO2 but there isn’t any compensatory increase in pulse to account for that rise in CO2 or the dilation of the arterials so they get cerebral hypoperfusion but at the same time their – the extravascular spaces, those are the collaterals and the increased venous hypertension can give you papilledema. And in this child just taking out the adenoid and tonsils got rid of his papilledema and causes his VEP to increase and improve. So that’s a shift, a paradigm shift in looking at these children.

So let’s have a look at this flow as to why they may get optic neuropathy. They may get optic neuropathy because of craniocerebral disproportion, that’s a small number, hydrocephalus, but then this combination of anomalous intracranial venous sinuses, obstructive sleep apnea can all lead to hypoxia because of cerebral hypoperfusion and also raise intracranial pressure because of raised intracranial venous pressure – hypertension. If the optic nerve head is anomalous because of these sheath changes then they get no disc swelling and in fact they are at greater risk of optic neuropathy and if they get chronic swollen disc they are at risk of optic neuropathy.
Take a moment and look at that flow and while you are looking at it just look at where I’ve put obstructive sleep apnea. If you have a child who has difficulty breathing because of narrow airways what do they do? They breathe harder. If they breathe harder what do children do? They sweat. If you are sweating and you have amblyopia in your left eye and you are trying to put a patch on the right eye to improve the vision in the left eye if you have a sweaty face guess what, the patches don’t stick. And furthermore, if you have shallow orbits the lashes and the eyeball get touched by the patch and the child doesn’t want to wear patches. So in children who have amblyopia and I’ve already explained to you and shown that they have an increased risk of amblyopia, if we are going to treat them, if we are going to treat them for their amblyopia we need to use atropine penalization.

Just for a moment think about those children that you deal with who have asthma, those children who have for some reason an extra respiratory effort who don’t have craniosynostoses but may have amblyopia, how many of those children do you normally give patches to? And now having learned this experience in the craniosynostotic children, we take it to another group of children who may not benefit from a patch because they have sticky – wet faces. Now think about the children who have eczema and automatically it’s a natural jump to say we don’t use patches in those children. We use atropine. So something that I learned from the craniosynostotic children I took to these other children and actually I should have realized it previously but I didn’t, I had to see it in these children to start thinking about other children who might have this – a problem that causes them to sweat more and therefore need another treatment regimen for their amblyopia.
So the surveillance protocol that I’ve been using since 2000 relies on aggressive amblyopia management including getting special glasses to fit the facial characteristics of these children, and atropine for patching and includes a combination of optic disc appearance with visual evoke potential. Now the two together have led to a directed craniofacial surgical intervention including ENT intervention. And what I mean by that is there are some children where you take out the adenoid and tonsils and the tissue regrows. The more you take it out the more it regrows, so you might have to go to C-Pap to try and improve their oxygenation, and that has a direct effect sometimes on how the optic nerves and visual pathway is functioning.

So when I see a child with craniosynostoses I don’t just look at the optic nerve head, I say to myself what amblyogenic factors does this child have? Does this child have strabismus? Does the child have anisometropia? Does the child have meridional amblyopia? Does the child have exposure keratopathy? And then I say what does the optic nerves look like? And I ask the parents, does your child snore at night? If you have a child under the age of 8 who snores that is not normal. That is not normal. And you want to explore whether when the child has a bad night of snoring how tired and lethargic that child feels the following day because remember if you are getting hypoxia and hypoperfusion that’s affecting the visual pathway then it’s affecting the whole of your brain, and we want to get in and stop that happening so the development and the natural global development of these children is not affected.

So you know what, it’s all talk. The question is does this surveillance protocol make a difference? So I did a retrospective case review between 2000 and 2003 so I had a minimum of 8 year follow-up,
or sort of a minimum of 5 year follow-up and we looked at the statistical comparison of visual acuities obtained with previous published departmental data. We have 60 patients in that time, 25 were syndromic and the mean months of age at presentation was about 16.2. In the first study that I showed you where we showed there was visual loss in 141 syndromic cases, the mean age was 23.3. So the age is about the same. The mean new cases per year in this new study were 6.25 and in the old study 7.05. You’ll see here that in our current cohort the amount of Apert’s and Saethre-Chotzen are the same, Crouzon and Pfeiffer the Pfeiffer a little bit less, the Crouzon a little bit more. So again a similar mix. And this is what we found, that the best eye corrected visual acuity was worse than 0.3, which is 20/40 in only 19% of children, whereas it was 40% in study 1 cohort. Using the Pearson Uncorrected Chi-Squared Test this is a significant change.

So conclusions. Visual loss in craniosynostoses is multifactorial and careful visual surveillance of children with craniosynostoses using this protocol has led to an improvement in visual acuity. Here is the thing, there is a lot been said in all, in neuroophthalmological circles how in raised – in idiopathic intracranial hypertension does sleep apnea play a role? And we know that in some children with idiopathic intracranial hypertension the optic nerves don’t swell. Well maybe we need to start looking as to why that doesn’t happen and maybe there is a common cause, a commonality between the two groups; however what is clear is that you can use VEPs to do surveillance in idiopathic intracranial hypertension like you do in craniosynostoses and look for a deterioration or improvement with the treatment modalities that we are using in idiopathic intracranial hypertension.
I want to thank you for listening to me and I hope that you’ve enjoyed this talk about a protocol for visual surveillance in craniosynostoses.