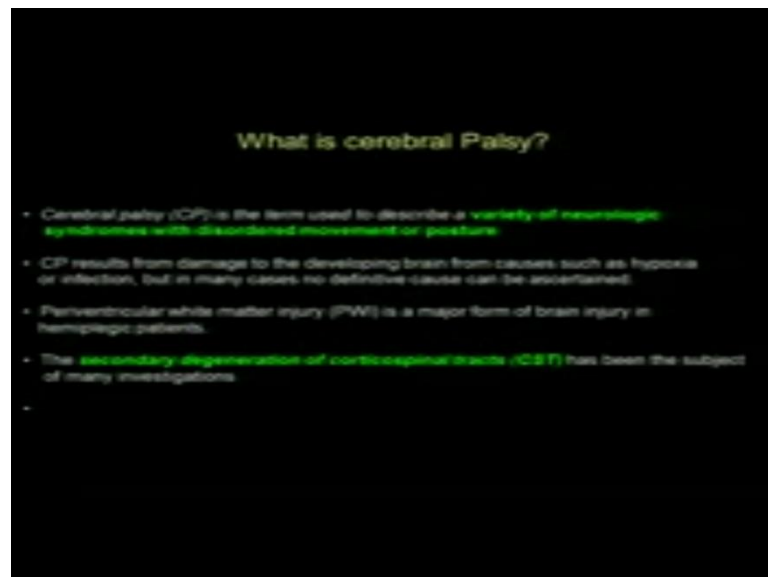


Selected Topics in Psychology
Neuropsychology
Prof. Rakesh K Gupta
Department of Humanities and Social Sciences
Indian Institute of Technology, Kanpur

Module - 5
Lecture - 25
Brain Microstructural Correlates of Cognition in Cerebral Palsy

Now, another important thing which I am wanted to cover is cerebral palsy which is very common all over the world.

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And the cause of the cerebral palsy could be early result while the child is developing or the result prenatal result when the child is coming out. An insult to the brain during delivery results in the damage of brain and irreversible damage of brain and both have different behaviour patterns different pattern. And in India we get another condition that where you get a cerebral palsy in the premature delivery. The child is born is sixth month the child is born is 7 month then the children are being cared in outside the mother's womb for 2 and 3 months more become they become like a normal individual. They also suffer a lot of damage in the brain, because they are not used to live in the environment you know. So, quickly, so early and that is the reason they get a lot of suffering to the brain. And it is a pathetic situation actually to something which you can correct something you can prevent. Especially the intrauterine when the child is lift at very

bottom the child is being delivered caught round the neck. The child does not cry after birth immediately after birth you know it is relevant important actually. The poor births have a delivery especially in this country even today, and there are responsible for large amount of cerebral palsy in this country.

Now, what is cerebral palsy that is the question which will be important for us to understand? Cerebral palsy is a term used to describe a variety of neurologic syndromes with disorder of the movement or the posture. It depends on which area of the brain is affected. If the cortex is affected then they develop seizures they have a mental decline. In the white penetrates are effected they classically develop more tendons function people say they have a sensory follow up by motor dysfunction say motor follow up by sensory. We have shown I will show that how the sensitivity takes over the motor and finally, the motor comes in. So that the second thing the third thing they develop are momentous hormones, because of the involvement of the basal ganglia what we call the carbo strike or basal ganglia that is the one which is responsible for the momentous disorders in children. And the fourth important thing is epilepsy. So, it is and they are not reversible whatever result occurs in the beginning of the life it does not worsen it does not improve. That is how you define the cerebral palsy. In the neurological condition there is a decline at the function of age as the pathology increases.

But whatever result here has occurred stays with you now we have to define like that girl asked yesterday rehabilitation. So, this is where the rehabilitation is important in children you know and this is a whole exercise that we are trying to do and some of the very rich people have the children of this practise. So, it is now, a disease of the poor of course, poor are involved rich are as much involved as the poor in this. So, it results for the damage to the brain developing brain from causes such as hypoxia or infection. But in many cases no definitive cause can be ascertain, but mostly it is an infection intrauterine infection, prenatal infection prenatal hypoxia. The indigenous white matter the per ventricular white matter. It is a major form of brain damages seen which you can see actually with normal eye and if at all over ultrasound and neutral of so and so ph1. And these injury result in the secondary affection of the tracks degeneration of the tracks what you call is the vulnerary degeneration or degeneration of tracks? And that is why we as a radiologist become interested in CP, because you most of the time the imaging will not

be abnormal. You find abnormal imaging in 20 percent of patients or they have spastic CP how do you understand how do you define them?

If you know if you see an imaging abnormality yes the CP is there if you do not see it is not CP do not you have still CP. So, what are the methods by which we can define cerebral palsy beyond the conventional disease and is there any way we can understand the neuro rehabilitation or what is called brain processor. How can we objectively asses the brain processory? So there are 2 issues which I will like to address in this particular talk, because when you give exercise therapy or kolstad therapy or botulinum therapy combined with exercise the child improves. But is the improvement is child commensurate with the improvement of the brain function or the re arise of the brain what is called a brain processing that is important. The proof of concepts comes from objectives assessment on the changes of the brain where there is a critical improvement in the patients that what is important?

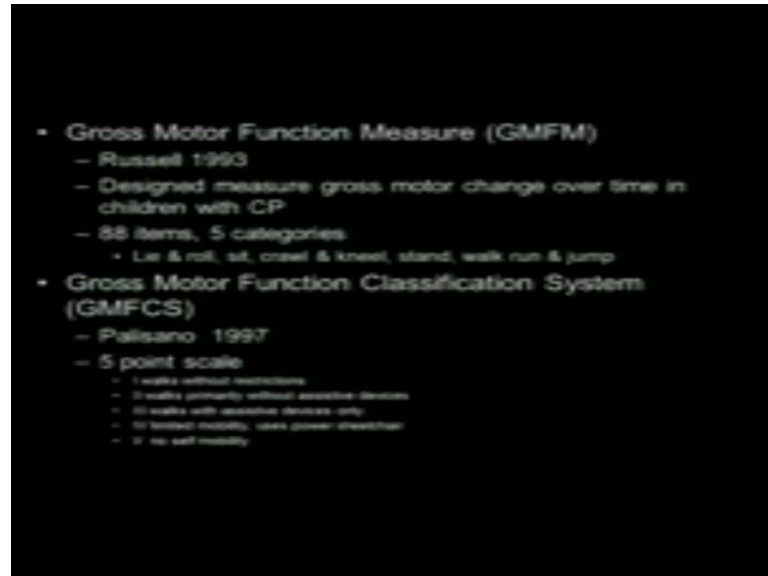
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<u>Motor Abnormality</u>	<u>Location</u>
Spastic	Diplegic
Dyskinetic/Choreoathetotic	Hemiplegic
Hypokinetic	Quadriplegic
Ataxic	Monoplegic

Now, this is a classification which has been described depending upon the abnormality like spastic. CP hemiplegic depending upon which area of the brain is affected quadriplegic mono pelagic all these things. And all which I have recite that I have mention to you we have recite the motor function there is a congression which goes of the epilepsy comes in the mono disorder comes. They all come into a part of they are part of CP different kind of CP whichever of areas of the brain is affected inner cell that

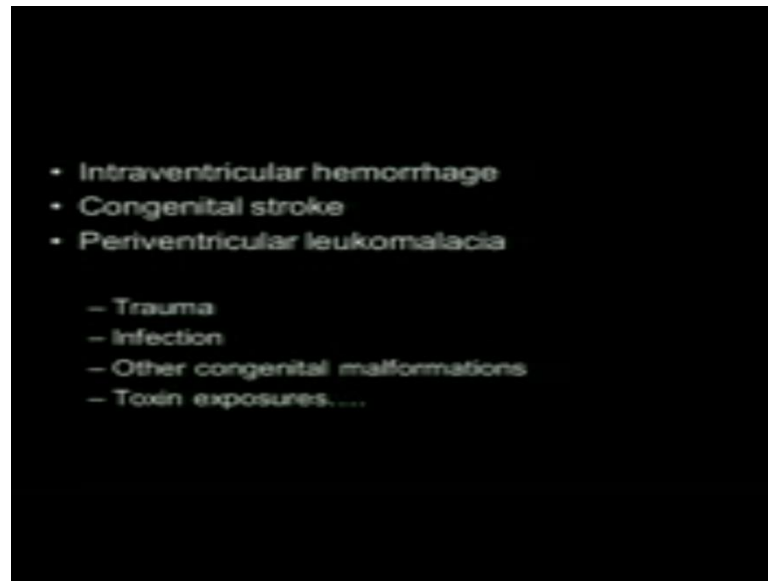
is what effects this you know cell and this has got something which is reversible. There is a reorganisation not reversibility that is the difference you know.

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The people have designed different tests to quantify the motor dysfunction GMFM score the world which is again we are ruled by the western world. And therefore, we follow them and you write these things no there is no issues they will not they will not question you anything you know. So, this is GMFM score and GMFCS score gross motor function classification system. So, these are one which has been designed by the western world and this is what we follow all of us for the CP classification how many deficits is there?

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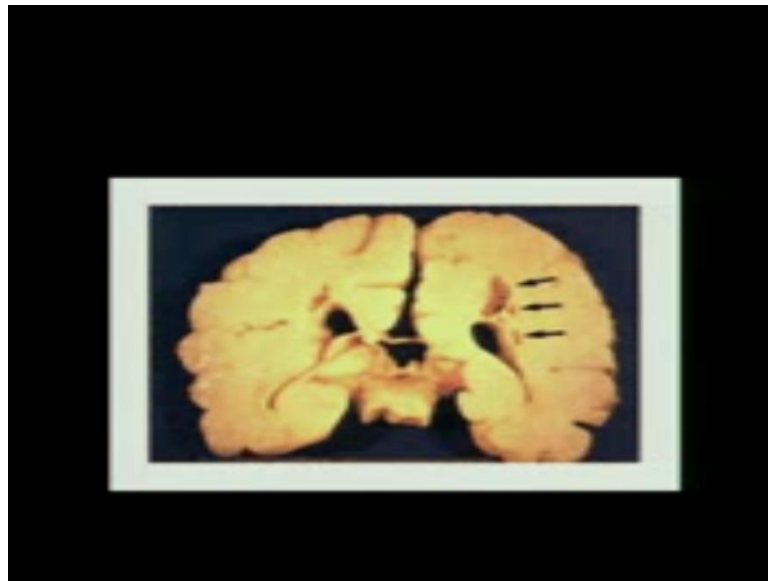


As I mentioned to you the cause of CP or intraventricular haemorrhage specially seen in the premature delivered baby. Congenital stroke means when the child is born he had a stroke the artery is blocked may be infection, may be crusion whatever the reason maybe. And another 1 per ventricular leukomalacia which is classically this is the 1 which is 1 is important. This is seen in a per neural hypoxia this is typical to India most of the India you know. What could be the reason? The reason is mainly the reason per ventricular leukomalacia is the peri pardon insert to the child when the child is being delivered there is muconium aspiration. And they are caught round the neck or the child did not cry whatever reason that is how they develop this hypoxia inter pardom and peri pardom you know. So, you so many times you may be hearing u know as a general population. The caesarean is required as the child is in distress and this is the way they make money the gynaecologist make mly. You know while saying that oh child is under stress and I want to take it out to prevent the eternity damage of the child. But the fact remains we call it as the gynaecologist is distress rather than the child distress.

Because she is in distress she do not want to come in the middle of the night deliver a child she will have a dinner take out the baby go home and sleep. And that is where you rely onto see that is really a child is distress or we protect the child birth interest. Now, they are doing this kind of exercise. Do we have petitioned to take care of the baby at that time as the child is coming out into new world in an environment? You know from the actual environment they are living in for 9 months. It is a different world all together

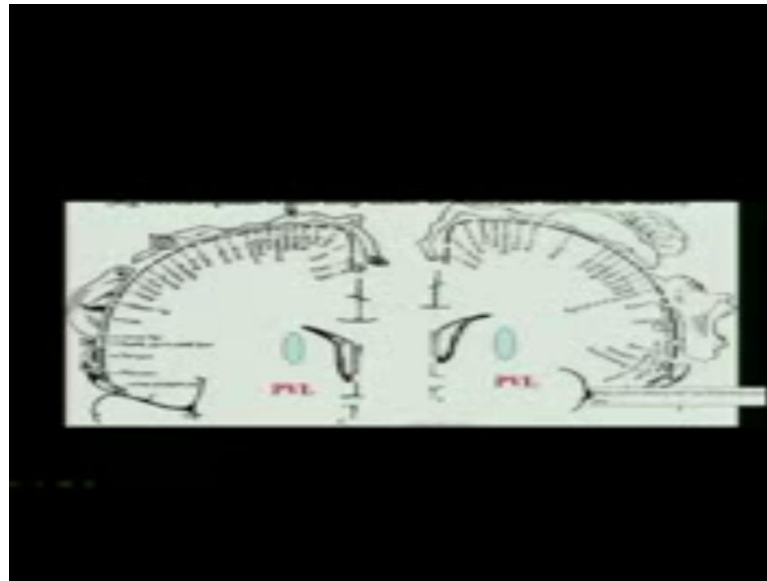
for a child you know the temperature is different, the oxygen is different, the feed is different everything is different for the child you know. So, that is what makes the difference you know for this. There are typically the describe the cause like trauma infection toxin exposures like a lot of overload overtake alcohol. And they are pregnant they can damage the child brain nerves. In India that is may not be true, but western world yes it is a common practise and we can do that.

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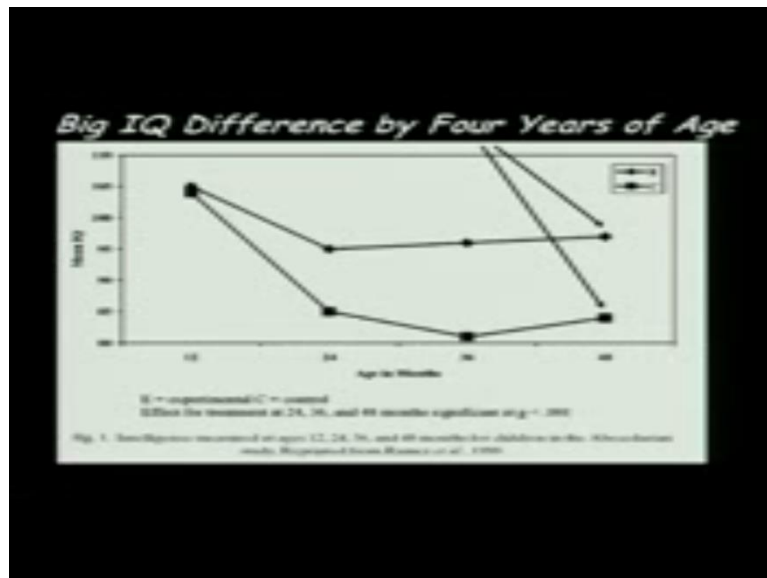
So that is how the periventriculation looks like on the contain surface the brain is damaged you can see it here, you can see it here, you can see it there this how the brain look like? Accumulation of soft brain in an area of glacises and it been all the cortex, it been all the basal ganglia and on thalamus any area depending upon what the child itself had at that time you know.

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And depending upon the area the child develops the neurological deficits. Motor sensory basal ganglia involvement cordial involvement epilepsy. It all depends on what where the initial is in the p v l or this area. Then and the p v l means the fibre's are going there you know and the fibres get cut connection is lost and they become you know spastic.

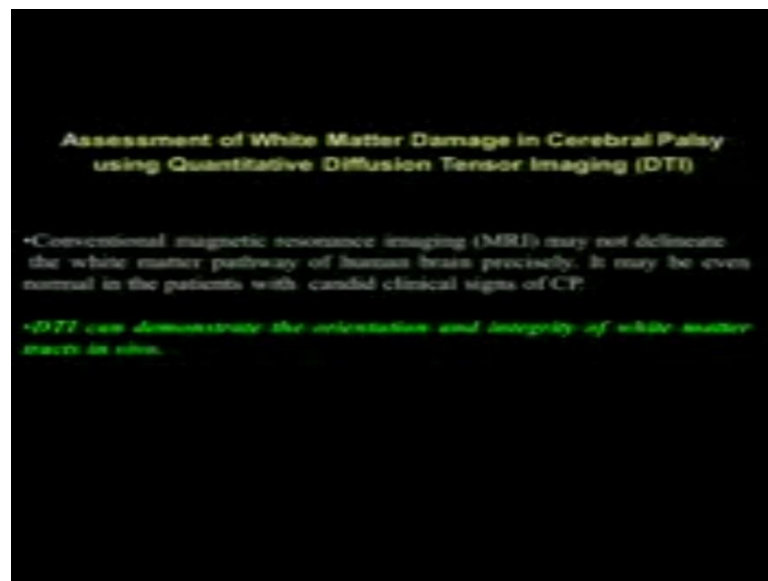
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Now, this is a interesting slide again from 1998 it is not a new thing which I am talking about most things are known. We have only objective as it and source of it we are inventing first time in the world no there is something we all know about it you know

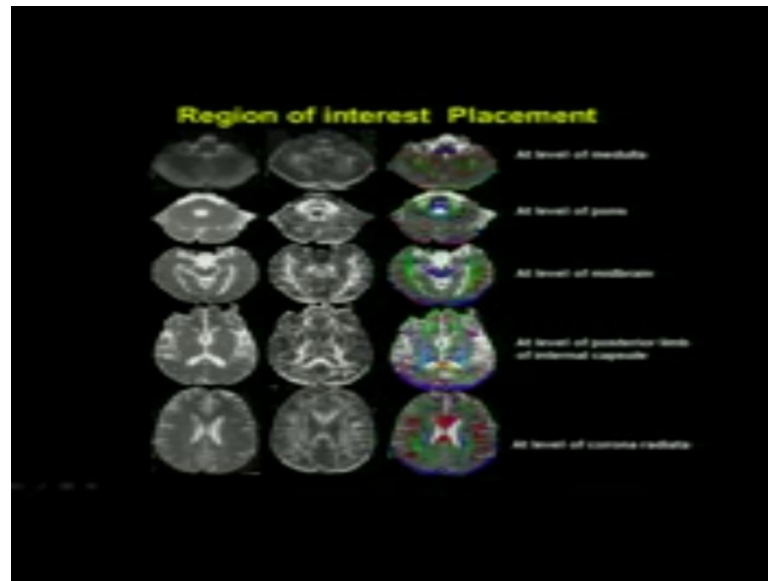
when a child moves from 0 to 36 weeks is of 36 months and 48 months the CP children have a decline in IQ as compared to a normal child they have decline in IQ. They will improve in IQ stabilization and there is a decline IQ about 1 year. And I call if you take a child with an IQ of 80 or 90 with the CP than I am not worried about at least the gross IQ changes you know in the brain spastic. So, we did that exercise also you know to see that I like your facts this girl actually worked on the 1 you gave she worked on that actually with us.

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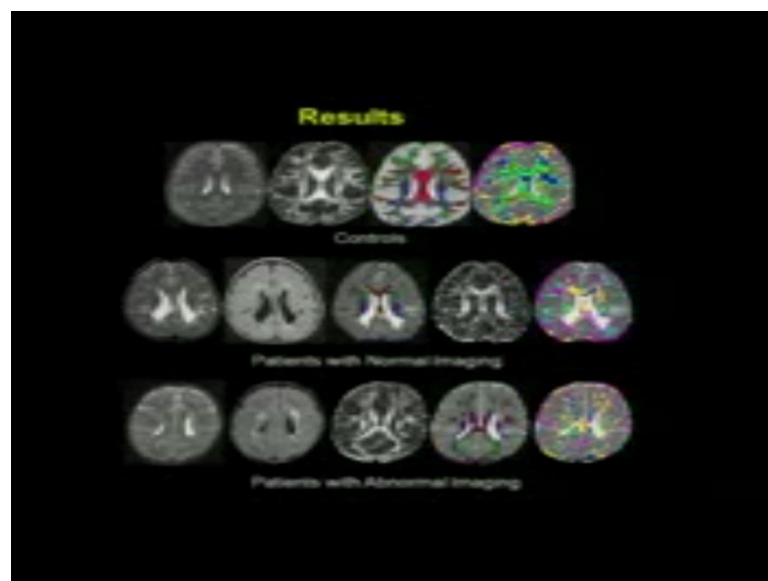
Now, our purpose was that can we assess the white matter damage in the cerebral palsy using quantitative diffusion tensor imaging. That is the one which we started in 2004 2005 and I think Ritcher Trivedi was first student she started working on that with us did PHD on this. The conversion arrival miss a lot of CP's, so we thought let us look at the tracts directly let see what are the damage to the tracts.

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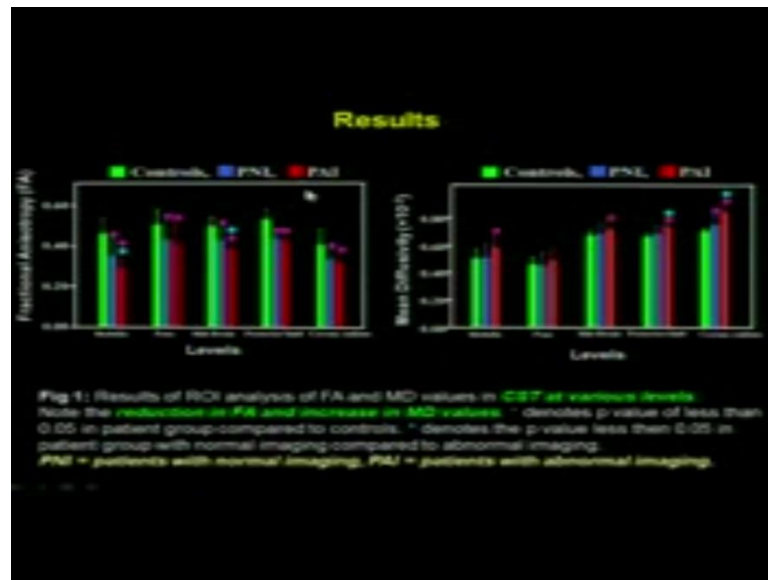
That is how we started in 2004-2005 getting that the d t i images f e values the colour coded f e values. Because at the tracks at the posterior limb of the internal capsule at the interior level of the internal capsule the corpuscular the white blooded tracks clearly define. And we put the region of interest actually in these areas that is how we try to solve in 2004-2005 and then we started realising that that is not the whole truth. We are only taking particular region and then trying to see rather looking at whole truth that is the way detectography and all start coming from them.

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So, these are the results on imaging and controls normal imaging and abnormal look at these periventriculation can you see the white segment here. This is classically described as periventriculation. This is definitely CP i do not have to do anything just look at the image and say cerebral palsy no question then why all this we are doing here?

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Now, this is a comparison of normal imaging and abnormal imaging. So, red is abnormal imaging and blue is a normal imaging CP and the control is the green. So, what you find is there is a decline as you move from green to red in the f a values. Irrespective of you know the location medulla the pons the mid brain posterior limb and the corona radiata and the m d value again showing increase. So, that is the first people actually we publish actually and saying that the involvement of the tract is there. Even if the imaging is normal that was the message when the image is abnormal I do not have to do this exercise. But if the imaging is normal there is reverse file looking at this and seeing that there is definitely CP you know.

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Results

Table 1: Quantitative mean and standard deviation of the DTI from the white matter tracts collected from the 12 subjects (normal controls) and 12 children with cerebral palsy.

ROI	Controls (n=12)	CP (n=12)	DTI (n=12)	DTI (n=12)
FA	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
MD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
AD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
RD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
MDSD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
TK	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100

Table 2: Quantitative mean and standard deviation of the DTI from the white matter tracts collected from the 12 subjects (normal controls) and 12 children with cerebral palsy.

ROI	Controls (n=12)	CP (n=12)	DTI (n=12)	DTI (n=12)
FA	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
MD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
AD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
RD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
MDSD	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100
TK	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100	0.2500 ± 0.0100

So, that was the first purpose we had these are the numbers just i show you the numbers are abnormal and we concluded that the changes are widespread and the tractography is superior than conventional m r i. Because you can pick up the area which are abnormal on d t i which are not seen in conventional m r i. So, then we moved beyond that and said we left together tracks.

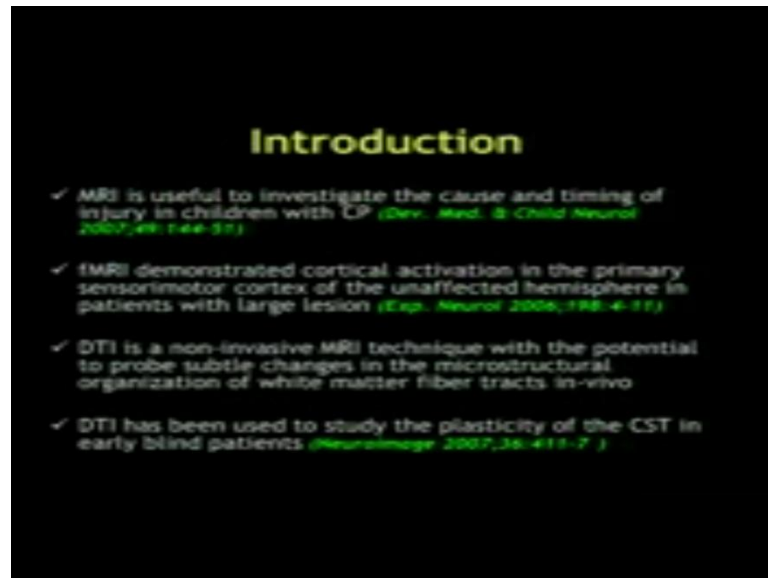
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Quantitative Diffusion Tensor Tractography (DTT) of Motor and Sensory White Matter Pathways in Cerebral palsy

So that is when the tractography came came into picture and we follow the tracks in cerebral palsy. And the issue was is the sensory fibres involved first or the motor

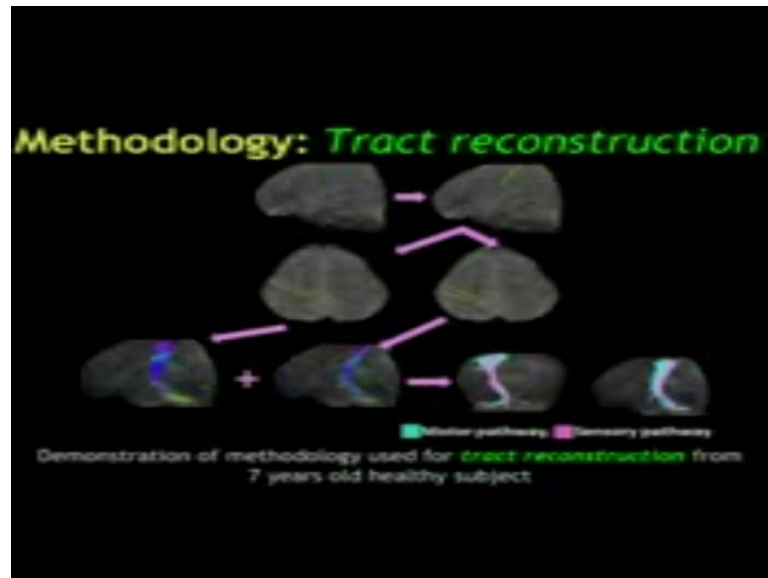
involves first. Because CP is a motor disease, but affection in the sensory and the motor is secondary this is the debate that is going over. First review given by a neurologist just while we were working on this and they give the first people 3 or 4 cases actually and we showed they showed the sensory involved earlier than the motor. And we of course, we did confirm that we as usual delayed in writing as compared to the western world.

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And this the just I showed you that the plasticity of the CST as is shown by DTI in the blind subjects actually. So, earlier review said the r o i analysis is to use and then we decided to do quantitative analysis.

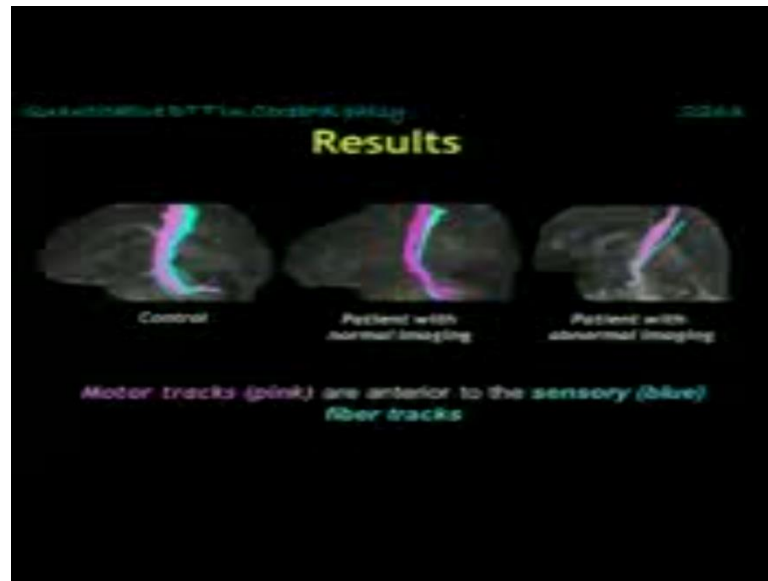
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To see the difference in this population. Now, this is the mapping we use for a sensory and motor r c verge still automated this there is something which I have been telling him to automate this which we have not done. So, far little challenge in doing this, but it can be done that is not something very big people have tried and done this in the western world. And we should be able to do it and implement the same here there is something which we are lagging what we doing is we just look at the centre circles and derate the centre surface.

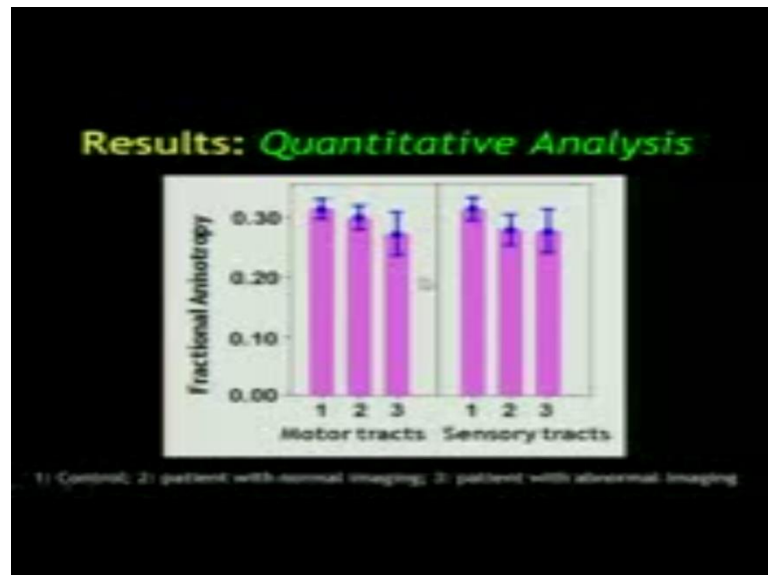
And border cortex and that is how we identify centre circles put the region of interest on the by hand that is the that is the trick here. So, this is anyway subjective that is the only part that we have subject in our tracts. Look at all the 3 plane axial and crawl ceretal and then create the sensory in the motor tract. So, centre circles on this side of centre circles is surgery strip on the interior part is a motor strip. So, that is how we generate the sensory and the motor they will give different colours to this so motor pathway and the sensory pathway. There is something called cells supplementary motor area we were talking about supplementary motor cells. We are talking about looking at the pre and the post central areas actually we will need this. But this area needs to be worked out by ourselves when the rest of the world.

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Well, this is the results of the patients versus controls with the normal imaging with the abnormal imaging and look at the tract difference. Since, we sensory is more affected than the motor right away you can see that. This was actually shown by on imaging note tractography by the first people and that they claim that actually.

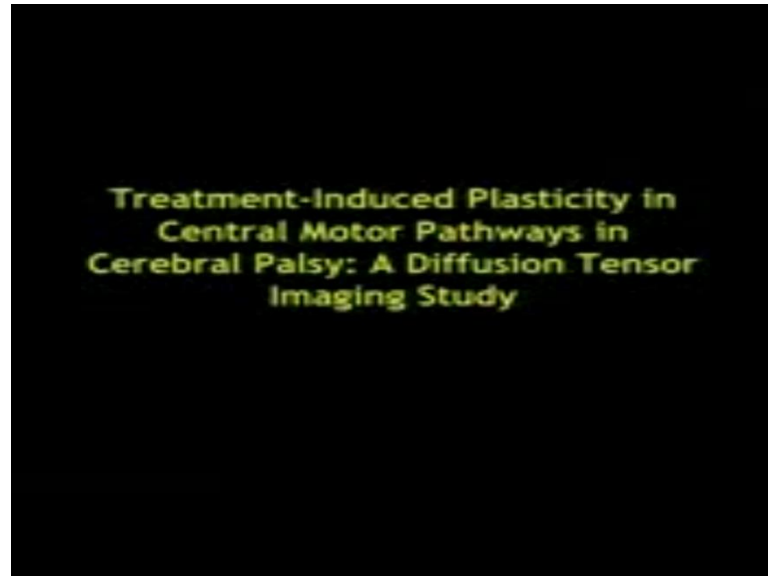
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Now, that is the result that is showing very clearly that how the quantitative analysis shows the sensory the motor abnormality. And we could actually classify the grade of the CP by the tractography. The cerebral people population and it could classify the grade of

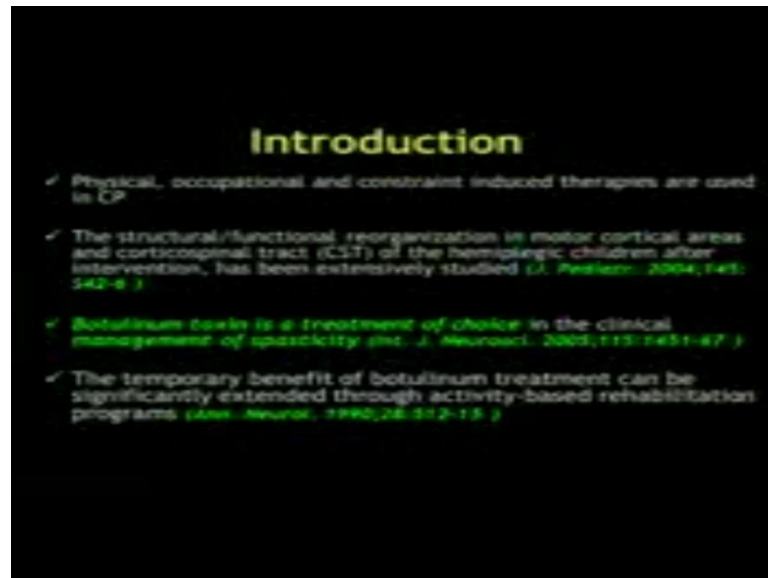
the CP based on the tracts only all sensory and the motor how much grade weakness like GMFM score and always you talked about we can actually grade them.

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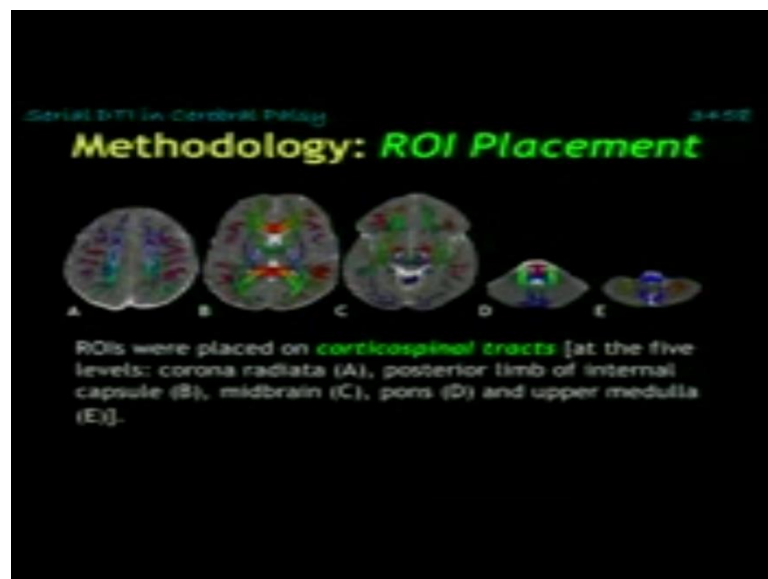
Now, this is important the treatment-induced plasticity. So, when we started treating them with botulinum and physiotherapy you know botulinum is expensive chemical you know. So, everybody cannot afford in this country botulinum and though they sell their house to help the child to have a you know small improvement in these functions but it may not always impossible. So, initially what we did we combine everything we had we combine physiotherapy botulinum what we could not give we could not differentiate. We are looking from the point of view of how much plasticity improvement is there in the brain improvement, in the clinical function how does it affect the brain function brain structurality you know what?

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So, this is what we tried.

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And see what botulinum does is botulinum reduces the spasticity of the muscle. So, when the muscle is spastic it difficult to do exercise. You know there is a coagulant kind of refractory you know you cannot move that that well when there is flaccidity the muscles can be moved quick back and forth with the b1 quickly you know. So, exercise effect is much better those as botulinum effect lasts for couple of months they lasts for the whole life. But that is window gives you window to improve the exercise that is the whole

purpose of doing the botulinum and physiotherapy what did it cost? It cost a lot of money in many 1 need 1 injection 2 injection you know and so and so which is describe the population which we have it will only possible. So initially did ROI analysis you can see you put the ROI on the posterior limb of internal capsule pons and medulla.

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Case	Age (years)	Sex	Clinical diagnosis	MRI diagnosis	Clinical grade (GMFCS level)
1	4:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
2	7:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
3	4:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
4	12:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
5	7:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
6	7:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
7	4:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
8	7:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
9	4:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV
10	7:00	Female	Spastic quadriplegia	Spastic quadriplegia	Grade IV

And this is the story of the child children spastic quadriplegia most of them are quadriplegia that is the grade of the score. And that was follow up score in most children they showed improvement 4 to 3 for these children even the grade 1 improvement from 4 to 3 or 3 to 2 is important. If they cannot sit or they cannot stand is not standing that is the big achievement for them. And if they are they can stand if they start walking a few steps that is the big milestone for them I tell you. So, you can understand the how much child feels happy and how the parent feels happy about this. So, and this happens, because of the placidity changes that bring and the proof of concept came from matching.

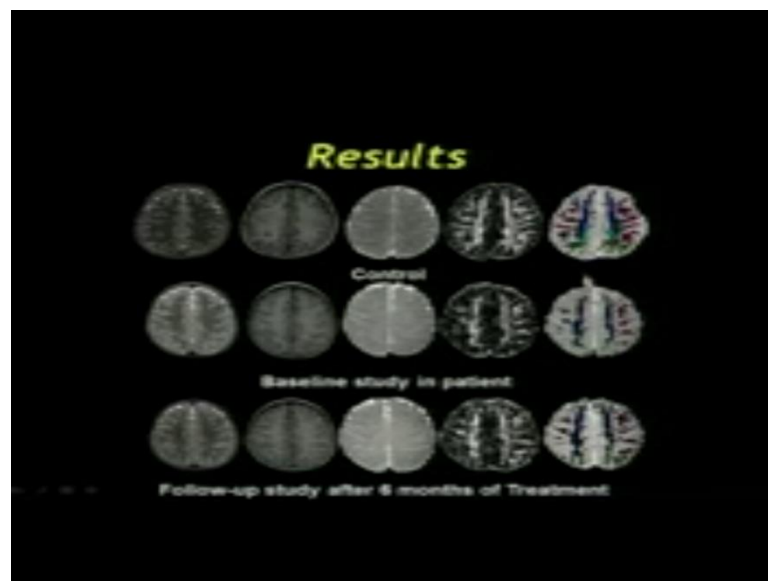
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Results: Demographic, clinical and conventional MRI data

Case	Age (years)	Sex	Diagnosis	Initial MRI (T1, T2, FLAIR)	At 6 months (T1, T2, FLAIR)	At 12 months (T1, T2, FLAIR)
1	12	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
2	15	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
3	18	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
4	22	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
5	25	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
6	28	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
7	32	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal
8	35	Female	Idiopathic Intracranial Hypertension	Normal	Normal	Normal

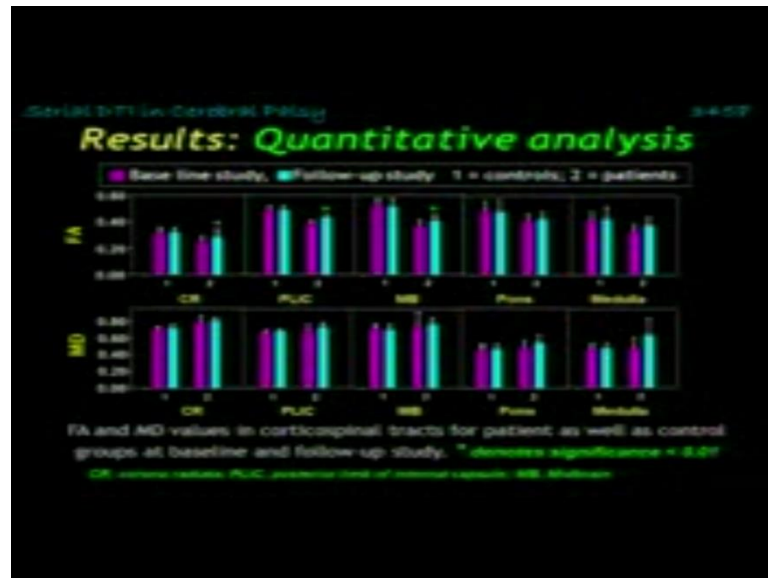
This is neuro rehabilitation which the girl was talking about.

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And what it showed clearly was when you look at this cingulum. Now, this is cingulum in the normal individual look at the cingulum 5 years here and they showed improvement on the follow up.

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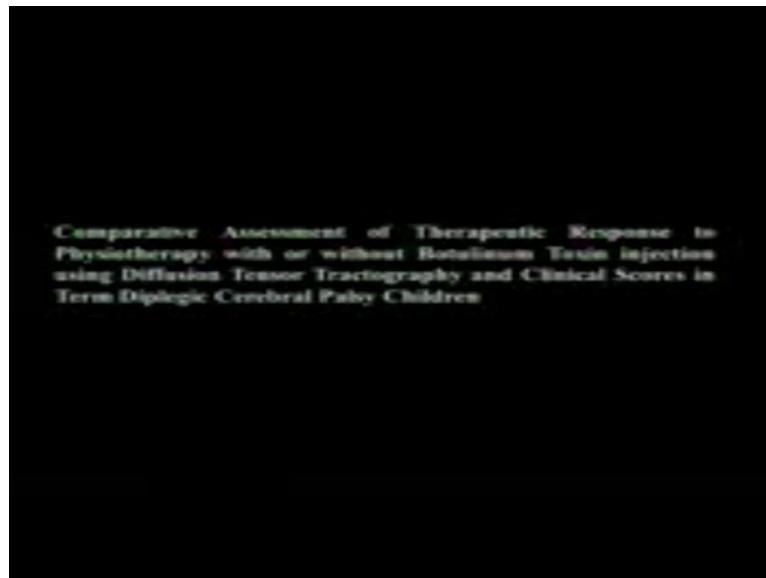
And of course, you can show that by numbers that there is a definite improvement in the mid brain, in the posterior limb of internal capsule, in the corona radiata. And this gave you the relationship between the change and the functionality of the child. So, child function was actually, because of the changes of the brain lot of local muscle power improved. So I only think that everything come from the brain that is what that is the proof of all thing you know here in this.

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- ✓ Increased FA in CST along with improved GMFCS score suggests that combined therapy increases functional connectivity in motor pathway in these patients.
- ✓ In the absence of valid radiological and pathological tests which can quantify treatment response in CP, clinicians have to depend on clinical tests and measurement tools which suffer from inter and intra observer variability.
- ✓ This may act as a guide in the objective assessment of therapeutic response in these children.

And similar thing we tried to show, so this is what we said at the end of the story that this may act as a guide in the objective assessment of therapeutic response in the children. Most people say that the child improved it is subjective So, objective wise the improvement you have to show the changes actual changes in the brain and that is what we showed the first time the changes are changes in the brain.

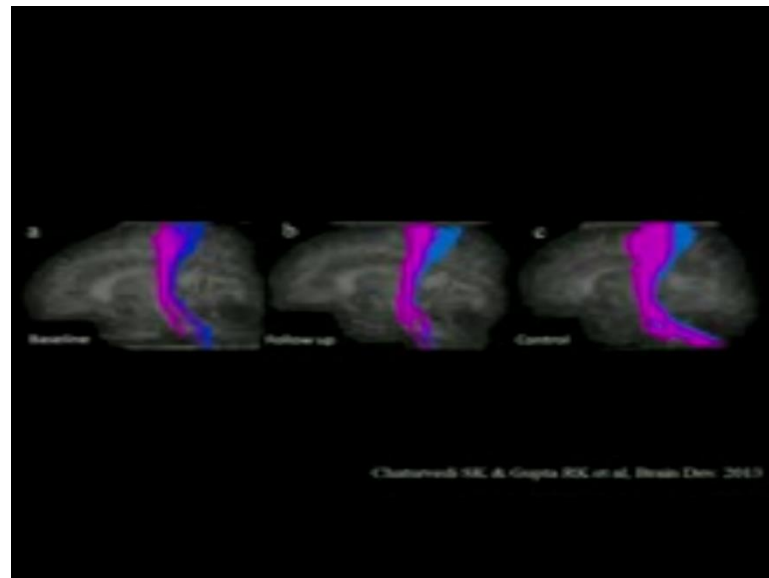
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Then the same question was that they were 2 questions which were raised from this study. There is a improvement in placidity is the botulinum required can we do without bortex can we do physiotherapy all or we combine physiotherapy and botulinum, because there is large a chunk of population which actually is deficient in money. So, they cannot afford botulinum they will keep the child leave the child and you know dump the child at times they get tired of this. The mother and the father get more tired of the child the child itself.

Because they carry to the hospital do exercises the child does not show much improvement according to them. A child sitting on the floor cannot start running at the most he will get up he will walk a few steps with the with the calliper or whether you know kind of things. And for some parents that are not enough they say they says carry for them you know whole life. So we decided to look at this we got a deviate where we try to look at this effective physiotherapy with or without botulinum and using tractography not the ROI analysis.

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So the same thing which we did earlier this is not published.

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Summary of comparison of mean of GMFMC value in baseline and follow-up of Group I and Group II

Group		mean±SD	
Group I (GMFMC)	Baseline	6.12±0.98	*0.000
	Follow-up	6.75±0.99	
Group II (GMFMC)	Baseline	6.44±0.19	*0.000
	Follow-up	6.56±0.17	

GMFMC, Gross motor and function measure; Group I, Physiotherapy alone; Group II, Botulinum plus physiotherapy

Chaturvedi NK, & Gupta RK, et al, Brain Dev. 2017

And the interesting thing was the, if you look at the 2 groups 1 group is with physiotherapy second is the physiotherapy with the botulinum. Both are showing improvement only with exercise and botulinum exercise both are showing improvement. So, as per as the improvement is concerned both are showing improvement then what is the benefit of b over a that the next thing we had I think we had discussed with doctor pandey our stratusthicion how to show the difference if it is there or not? Then this

illustrates the, what is called as the analytic of index of improvement change delta change or something divided by delta or r delta. And all these things so that was suggested to me by a couple of people in US actually I do not take this as a direct measures and create a kind of a delta difference between the 2 and that is what we did actually in this paper. And that took couple of years to publish it actually after the work was done primarily, because we were not sure on methodology what to do use in this you know and number of queries on this.

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Summary of comparison of mean of FA value in motor and sensory fiber bundle between baseline and follow-up of Group I and Group II

Group		Motor		Sensory	
		mean(SD)	p value	mean(SD)	p value
Group I (FA)	Baseline	0.22(0.05)	<0.001	0.22(0.05)	<0.001
	Follow-up	0.24(0.05)		0.24(0.05)	
Group II (FA)	Baseline	0.22(0.05)	<0.001	0.22(0.05)	<0.001
	Follow-up	0.24(0.05)		0.24(0.05)	

Chaturvedi NK, & Gupta RK et al, Brain Dev. 2013

Now these are the comparison of a mean f a value in motor and the sensory fibre between baselines and follow up. So, what we showed on the score zero score improvement the same thing is shown on the motor and sensory both are showing improvement in it. So, the plasticity changes are seen not only in the sensory but in both and the same was true in the botulinum group as well. But still does not answer the question, should we use botulinum or should we use do not use botulinum? You know now, that is where we are.

(Refer Slide Time: 26:18)

Summary of comparison of mean of FA value in motor and sensory fiber bundle between Group I and Group II in spastic diplegic children

	Group	Motor		Sensory	
		mean(SD)	p-value	mean(SD)	p-value
FA baseline	Group I	0.23(0.03)	0.96	0.23(0.03)	0.70
	Group II	0.22(0.03)		0.22(0.03)	
FA follow-up	Group I	0.26(0.03)	0.96	0.23(0.03)	0.40
	Group II	0.23(0.03)		0.23(0.03)	
FA Delta	Group I	0.027(0.03)	0.99	0.03(0.03)	0.99
	Group II	0.02(0.03)		0.02(0.03)	
FA relative delta	Group I	0.077(0.03)	0.96	0.07(0.03)	0.80
	Group II	0.077(0.03)		0.06(0.03)	

Chattervedi NK, & Gupta RK, et al, Strain Dev, 2013

When we compared the botulinum directly the 2 groups you know, because they were everything and iatrical except the botulinum and no botulinum. We took the subject over in the same grade, same psychology, same con concrete decline everything same and same IQ everything was we did change no epilepsy. So it is a very selective graduation we took just to assure that we do not kind of a con confirm over results based on that. And if you look at this there is no difference in the f a value in the baseline in f a value of the follow up. And then we did the delta the difference and there was no difference in delta and relative delta only you can see no difference in it. So, suggested there were that the botulinum may not be of much value except that temporarily it will cause flexibility where you can start exercising. But the end result in 6 months is same for both of these.

(Refer Slide Time: 27:18)

Summary of comparison of mean of GMFM value between Group I and Group II in spastic diplegic children

	Group I	Group II	p-value
GMFM baseline	8.72±0.86	8.44±0.79	0.14
GMFM follow-up	8.79±0.89	8.78±0.77	0.86
GMFM delta	8.86±0.89	8.85±0.89	0.70
GMFM relative delta	8.77±0.82	8.77±0.84	0.46

Chaturvedi NK, & Gupta RK, et al, Brain Dev. 2019

So, you can save money for this now this the GMFM score for baseline and follow up followed this improvement group 1 to 2 not significant, but still there. But critical score as well as the imaging score did show much difference you know together.

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Pearson correlation of FA value in sensory and motor fiber bundle with GMFM score

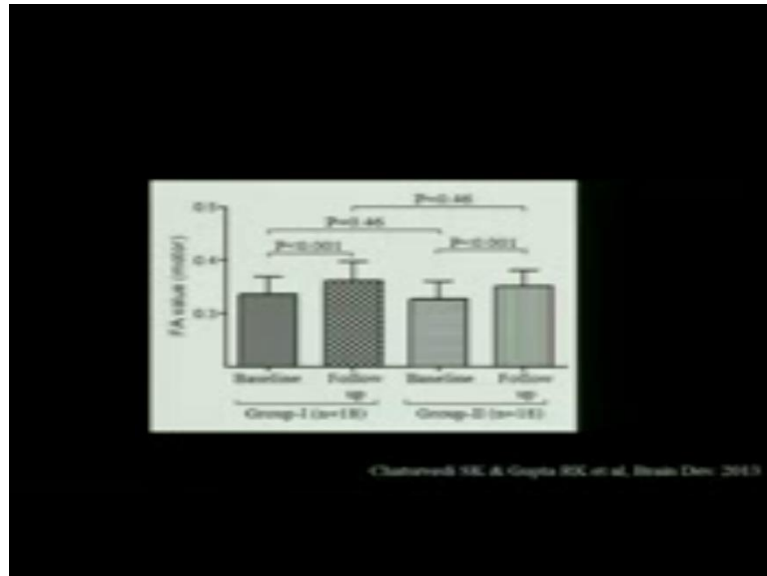
	Motor (FA)	Sensory (FA)
GMFM	r=0.642 p=0.017	r=0.660 p=0.012

Chaturvedi NK, & Gupta RK, et al, Brain Dev. 2019

Now, this is the sensory and motor bundle pearson correlation with the scores. This show relatively in correlation with the f a values of sensory and motor GMFM score actually so what we concluded by this study was that children with identical kind of disease may not need the botulinum with the big relief to the patients. So, physiotherapy done well is

as good as used in the botulinum sensory therapy together. So that was the question d s t wanted me to ask answer and we have answered his question.

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The next disease just a example you see in the graphics which we are trying to show same thing in the graphics which we are trying to show. Again this GMFM score whatever I have talked about in the table is the same thing shown in the.

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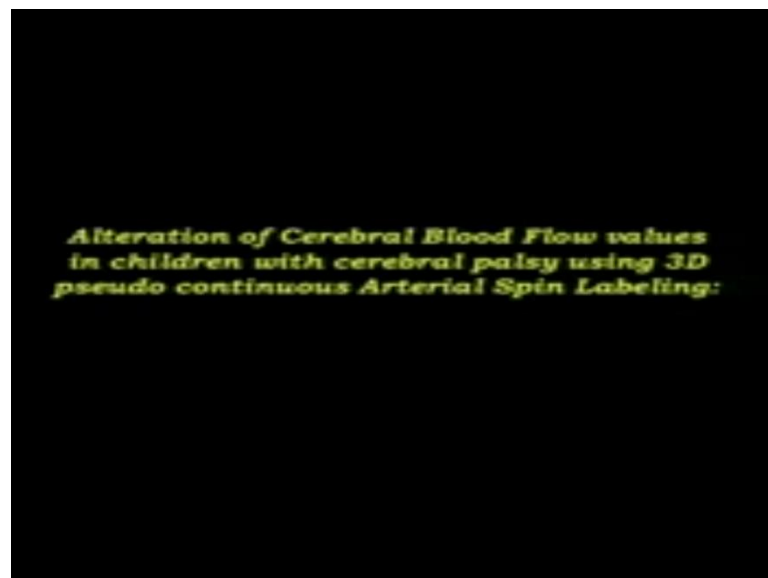
Now, this I added in the slide is all my slide there is a girl that considered too worked on Saturday in CP. And he has gone doctor cello work which I do actually on d t i also and

we had a lot of data from this group as shown the f c testing's made of money also which are not yet written and published. That is the next income I mean you need a lot of staff to do all kind of things data is there with us and you are welcome. If you want the data from us I will give it to you no problem in this somebody has to write this you know.

Now, this is an example of the functional MRI and 2 weeks treadmill training this guy specially works on the treadmill with children. He has specially designed that he has lot of funding in the western he does all kind of things he is a neurologist; he does this kind of things. And he has shown there is a improvement in the functionality here in these children we cannot do active exercise. If we do we do a passive exercise and it showed changes in the brain function by FMRI you know in this.

So what we showed on the DTI is again shown by the functional MR the placidity changes are there in the brain following therapy and its important. He is a believer of botulinum, because he is funded by the company you know for his projects. But for me I am funded by the government of India and I do not believe this, because I basically want to support the patient not support the company in this you know.

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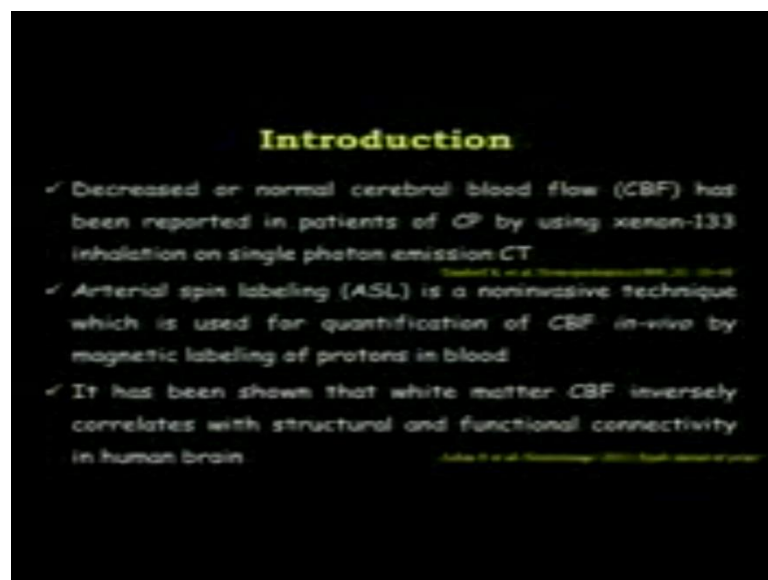


Now this is the last story I want to this another story we decided we handled it in a very sophisticated technique which we talked it about yesterday as ASL arterial spin labelling. See you are actually quantifying the flow of blood in FMRI bold cerebral blood flow in the valve and this method is being now, tried more and more in FMRI. So, we decided to

look at how the cerebral blood flow changes this we have submitted publication actually now. In these children there is repeated everything on the CP whatever you could do you know with our methodology we even tried FMRI did not work very well actually on this what is showing?

So, we are getting lot of odd defects in the data i do not know why we are getting data defects from this. So the basic why did we start doing the CP in the blood fall blood flow quantization I was personally interested to see my initial thinking was the blood flow should decrease if the area is damaged.

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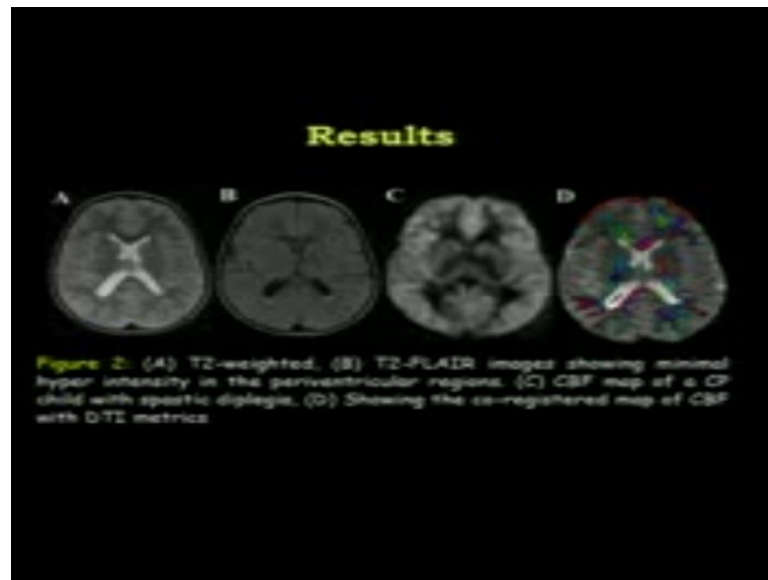


And this was decreased or the normal CBF has been reported in patients of CP using xenon 133 study in fact this was the question which was very critical and lot of people when we presented the data. And normally me other people also saying the same thing which I am saying it will be more thought that I am I have not done the right thing in right way. I told them I have done everything right what it should be done right in the world when couple of more people said the same thing then probably I was right.

But initially I had faced lot of criticism when I present this first time in the paper like sir manam lot of criticism came to me people were after my life this is how do you explain this how do you explain in this. Well, I said I do not know this is the observation I have done an alteration ASL is possible. Because it is a simple technique no radiation no non-invasive technique available and the CBF white matter inversely correlates the structural

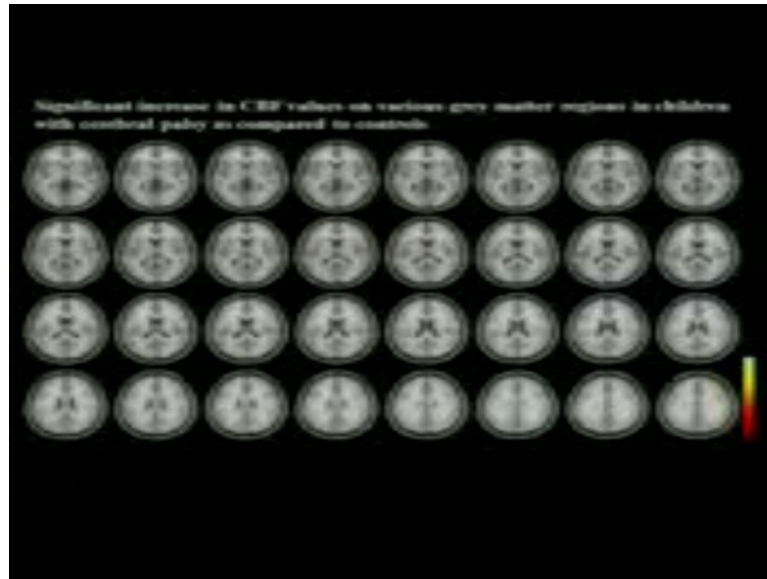
and functional connectivity in the brain. This has been shown in 20 level and that is the only thing I told them look there is a inverse relationship between the connection and the and the function of CP.

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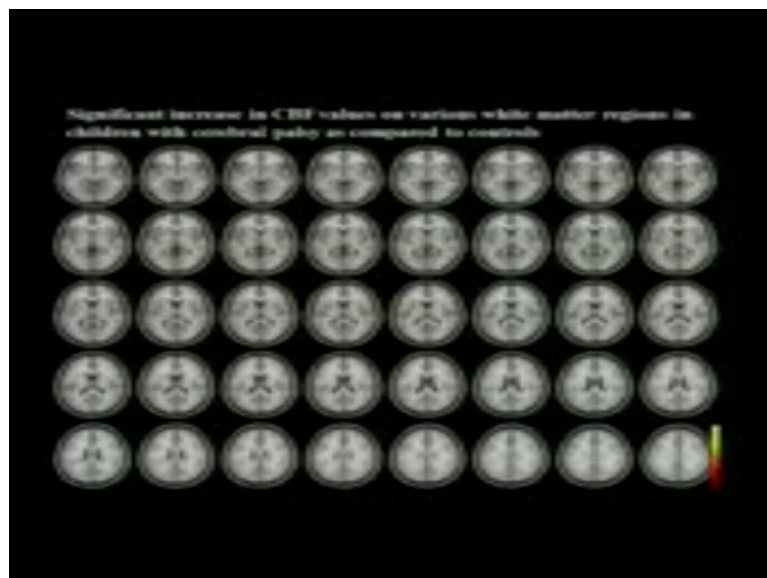
Now, this is how the ASL image looks like you have seen the DTIT 2 flair, but this is how ASL looks like. The white matter has low flow and the green matter has more flow that is what you expect right and that is what is beautifully shown on this. So, my issue was what we did it was co registered the data of the DTI which is done by doctor Varthur bring all registration this is whatever we want his him to do. And there issue was that whatever ROI we are taking is that a right way to or we should do a global analysis. So, I waited for particularly 2 years before actually I wrote the paper actually we have the data available with us then we did what is called AVBM analysis of this whole group you know.

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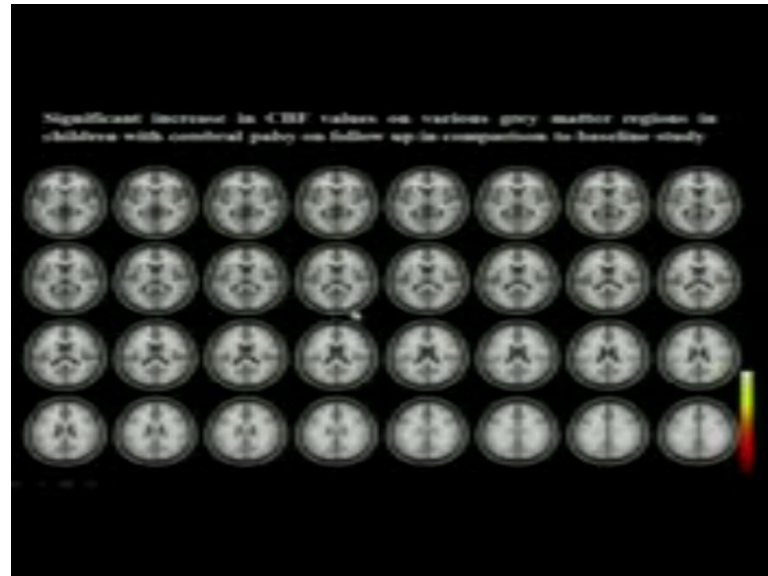
And this is the result of VBM analysis. Now, significant increase in CBF this colour you can colour scaling you can see this is point 0 0 1 higher significant differences seen. Increase significant in CBF in the grey matter has been shown not only white look at grey matter showing the changes the different images of brain. The CBF was increased even by the automatic analysis what we initially said was ROI analysis which I discarded, because they were very critical of whatever be.

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And these were the wide better changes as you can see that large number of areas is showing to the white matter now.

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Then what we did was this is the comparison of the follow up. Once we followed up the same children there was definitely a decrease in some of the areas you know there was the further increase in the areas you know in the grey matter areas. You can see there is a increase in the grey matter. So, the region the grey matter which were abnormal initially and what is interesting was there was decrease in the white matter area flow. It means the grey matter damage needed more flow in the 1 exercising how, but the white matter decreases in the some other areas which we have seen that in already analysis this is in six month following therapy.

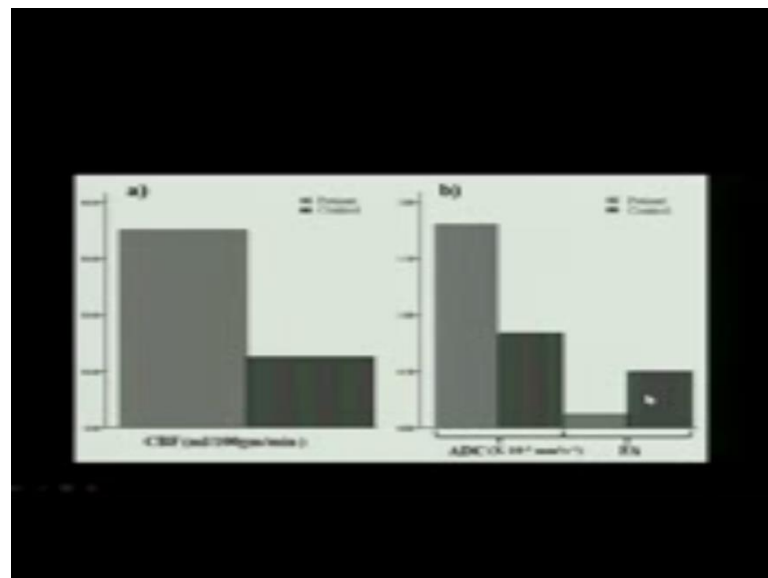
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Grey and white matter regions with significant changes in cerebral blood flow values based upon voxel based morphometry in children of maternal preeclampsia as compared to controls.

Region	Z	Cluster Size	Volume	Intensity	Significance	Change
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+
Precentral Gyrus	16.2	100	10.0	1.150	<0.0001	+

These are some of the numbers which we got from those coordinates that there is a increase.

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And you can see the CBF is definitely very high as compared to controls ADC is high and the f a is low, low f a and the high ADC very consistent notice.

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Grey and white matter regions with significant changes in cerebral blood flow values based upon voxel based morphology in children of cerebral palsy as follow up to comparison to healthy

Regions	Voxel coordinates			Z score	P-value	Changes
	X	Y	Z			
Precentral Gyrus	45	24.8	28.7	4.124	0.000107	↑
Precentral sulcus	45	24	28	4.124	0.000107	↑
Precentral white matter	44-6224	24-6224	28-247	4.428	0	↓
Supramarginal Gyrus	47.8	35	34	4.124	0.000107	↓
Supramarginal white matter	48.4	37.5	34	4.224	0	↓

So, this is the follow up comparison of the grey and white matter numbers what I showed you on the images.

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Grey and white matter regions with high cerebral blood flow in children of CP showing significant changes in values of ADC and FA values as compared to controls

Regions	Volume	ADC		FA
		CP (n=22/20)	Controls (n=27/20)	
Precentral Gyrus	Precentral	107.7500*	112.85	0.2800*
	Precentral sulcus	114.117	112.85	0.2100
Precentral sulcus	Precentral	75.7500*	112.85	0.2400*
	Precentral sulcus	80.2750	112.85	0.2100
Supramarginal Gyrus	Precentral	75.7500*	112.85	0.2400*
	Precentral	82.4250	112.85	0.2400
Supramarginal sulcus	Precentral	107.7500*	112.85	0.2800*
	Precentral	86.117	112.85	0.2100
Precentral white matter	Precentral	74.7500*	112.85	0.2800*
	Precentral	87.125	112.85	0.2100
Precentral white matter	Precentral	82.7500*	112.85	0.2800*
	Precentral	86.250	112.85	0.2400
Precentral white matter	Precentral	107.7500*	112.85	0.2800*
	Precentral	114.117	112.85	0.2100
Precentral white matter	Precentral	107.7500*	112.85	0.2800*
	Precentral	114.117	112.85	0.2100
Supramarginal Gyrus	Precentral	107.7500*	112.85	0.2800*
	Precentral	114.117	112.85	0.2100
Supramarginal white matter	Precentral	107.7500*	112.85	0.2800*
	Precentral	114.117	112.85	0.2100

Increase and decrease

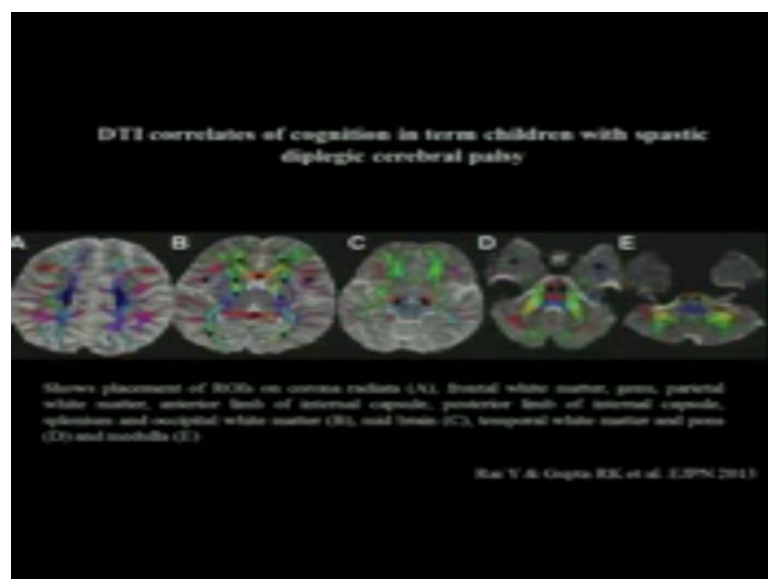
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AADC and FA values among regions with significant changes in CBF observed in white and grey matter regions in children of CP on follow up in comparison to baseline

Region		CBF (ml/100g/min)	AADC ($\times 10^{-3}$ sec ⁻¹)	FA
Frontal GM R	Baseline	43.847*	0.903	0.469
	Follow-up	42.118	0.966	0.473
Frontal GM L	Baseline	43.480*	1.270	0.476
	Follow-up	44.476	0.936	0.469
Parietal WM R	Baseline	44.440*	0.886	0.323
	Follow-up	45.176	0.887	0.329
Temporal WM L	Baseline	48.762*	0.884	0.279
	Follow-up	59.862	0.837	0.273
Temporal WM R	Baseline	49.897*	0.847	0.309
	Follow-up	56.232	0.876	0.301

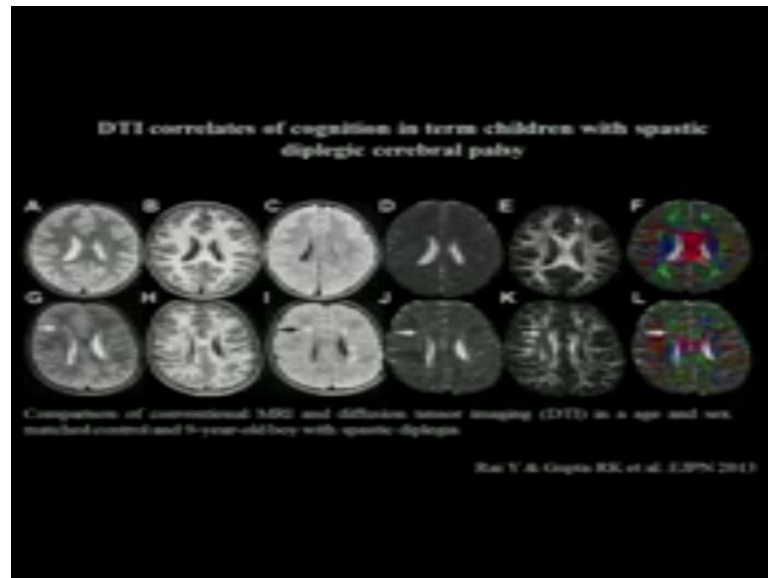
And what is interesting was in some of the areas where the CBF was increasing the f a and m d does not showed any changes. So, we concluded from this paper so only the CBF is a better measure of damage than the tractography. Because some of the regions we go went back with abnormal CBF to quantify the value of white matter f a value they were not really abnormal. May be a more suggestive indicator of the damage that is this that is what we try to conclude this paper actually.

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Now, this is the last with this girl actually she is the, for lead author in this she has very keen as a as a person and in competition. She said avoid writing in paper and note the not we are doing therapy and all the you know as she did all the exercise of doing the ROI analysis. This paper has come already in the European journal of paediatric neurology she had I think 4 or 5 peoples class in short time.

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Now, this is all I showed example how it looks normal and abnormal brain in CP.

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The figure shows a table titled "DTI correlates of cognition in term children with spastic diplegic cerebral palsy" with a subtitle "Summary of mean neuropsychological test scores in spastic diplegic children and healthy controls". The table compares scores between spastic diplegic children (n=22) and healthy controls (n=22). The p-values for all comparisons are <math>< 0.001</math>.

Neuropsychological domains	Spastic diplegic children (n = 22) (Mean ± SD)	Healthy controls (n = 22) (Mean ± SD)	p-Value
CIQOL	3.46 ± 3.22	37.68 ± 7.54	<math>< 0.001</math>
Executive	4.72 ± 4.41	30.76 ± 8.75	<math>< 0.001</math>
Memory span	4.82 ± 4.72	36.26 ± 14.2	<math>< 0.001</math>
Verbal reasoning	12.29 ± 4.25	22.22 ± 7.24	<math>< 0.001</math>
Mean	3.82 ± 3.26	30.26 ± 10.07	<math>< 0.001</math>
Learning rates	10.46 ± 4.25	33.69 ± 7.02	<math>< 0.001</math>
Quantity	1.22 ± 4.22	30.29 ± 8.27	<math>< 0.001</math>
Mean	1.28 ± 3.25	30.69 ± 10.25	<math>< 0.001</math>
Verbal IQ	1.28 ± 1.71	23.69 ± 10.07	<math>< 0.001</math>
IQ	12.22 ± 10.24	33.69 ± 10.24	<math>< 0.001</math>

†††† Significant relations shown in the table.
Note: CIQ, intelligence quotient.

Rao V & Gupta RK et al. EJPNe 2013

And this is the test I think which you have a copy and we gave you the same thing which I used in the children from 3 to 4 years to 10 years we had generally. And most of the range was in between 4 and 7 years as in this we excluded very different ranges of children in this group. And you now and you can see a significant difference in neuropsychology.

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DTI correlates of cognition in term children with spastic diplegic cerebral palsy

Summary of mean DTI metrics (FA and MD) in spastic diplegic children and healthy controls.

	Spastic diplegia (Mean = 507)	Healthy (Mean = 507)	p-value
FA	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001
FA _{ax}	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD _{ax}	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001
FA _{rad}	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD _{rad}	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001
FA _{ang}	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD _{ang}	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001
FA _{ap}	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD _{ap}	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001
FA _{cp}	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD _{cp}	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001
FA _{cc}	0.42 ± 0.07	0.43 ± 0.07	<0.0001
MD _{cc}	0.002 ± 0.0005	0.002 ± 0.0005	<0.0001

Rao V & Gupta RK et al. IJPN 2011

And these are the changes of course, you see in the f a values.

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DTI correlates of cognition in term children with spastic diplegic cerebral palsy

Pearson correlation of FA and MD values with NPT

	FA	MD	FA _{ax}	MD _{ax}	FA _{rad}	MD _{rad}	FA _{ang}	MD _{ang}	FA _{ap}	MD _{ap}	FA _{cp}	MD _{cp}	FA _{cc}	MD _{cc}
WISC-III	0.12	-0.05	0.12	-0.05	0.12	-0.05	0.12	-0.05	0.12	-0.05	0.12	-0.05	0.12	-0.05
WISC-III PI	0.15	-0.08	0.15	-0.08	0.15	-0.08	0.15	-0.08	0.15	-0.08	0.15	-0.08	0.15	-0.08
WISC-III VIQ	0.18	-0.12	0.18	-0.12	0.18	-0.12	0.18	-0.12	0.18	-0.12	0.18	-0.12	0.18	-0.12
WISC-III VIQI	0.22	-0.18	0.22	-0.18	0.22	-0.18	0.22	-0.18	0.22	-0.18	0.22	-0.18	0.22	-0.18
WISC-III VIQII	0.25	-0.22	0.25	-0.22	0.25	-0.22	0.25	-0.22	0.25	-0.22	0.25	-0.22	0.25	-0.22
WISC-III VIQIII	0.28	-0.28	0.28	-0.28	0.28	-0.28	0.28	-0.28	0.28	-0.28	0.28	-0.28	0.28	-0.28
WISC-III VIQIV	0.32	-0.32	0.32	-0.32	0.32	-0.32	0.32	-0.32	0.32	-0.32	0.32	-0.32	0.32	-0.32
WISC-III VIQV	0.35	-0.35	0.35	-0.35	0.35	-0.35	0.35	-0.35	0.35	-0.35	0.35	-0.35	0.35	-0.35
WISC-III VIQVI	0.38	-0.38	0.38	-0.38	0.38	-0.38	0.38	-0.38	0.38	-0.38	0.38	-0.38	0.38	-0.38
WISC-III VIQVII	0.42	-0.42	0.42	-0.42	0.42	-0.42	0.42	-0.42	0.42	-0.42	0.42	-0.42	0.42	-0.42
WISC-III VIQVIII	0.45	-0.45	0.45	-0.45	0.45	-0.45	0.45	-0.45	0.45	-0.45	0.45	-0.45	0.45	-0.45
WISC-III VIQIX	0.48	-0.48	0.48	-0.48	0.48	-0.48	0.48	-0.48	0.48	-0.48	0.48	-0.48	0.48	-0.48
WISC-III VIQX	0.52	-0.52	0.52	-0.52	0.52	-0.52	0.52	-0.52	0.52	-0.52	0.52	-0.52	0.52	-0.52
WISC-III VIQXI	0.55	-0.55	0.55	-0.55	0.55	-0.55	0.55	-0.55	0.55	-0.55	0.55	-0.55	0.55	-0.55
WISC-III VIQXII	0.58	-0.58	0.58	-0.58	0.58	-0.58	0.58	-0.58	0.58	-0.58	0.58	-0.58	0.58	-0.58
WISC-III VIQXIII	0.62	-0.62	0.62	-0.62	0.62	-0.62	0.62	-0.62	0.62	-0.62	0.62	-0.62	0.62	-0.62
WISC-III VIQXIV	0.65	-0.65	0.65	-0.65	0.65	-0.65	0.65	-0.65	0.65	-0.65	0.65	-0.65	0.65	-0.65
WISC-III VIQXV	0.68	-0.68	0.68	-0.68	0.68	-0.68	0.68	-0.68	0.68	-0.68	0.68	-0.68	0.68	-0.68
WISC-III VIQXVI	0.72	-0.72	0.72	-0.72	0.72	-0.72	0.72	-0.72	0.72	-0.72	0.72	-0.72	0.72	-0.72
WISC-III VIQXVII	0.75	-0.75	0.75	-0.75	0.75	-0.75	0.75	-0.75	0.75	-0.75	0.75	-0.75	0.75	-0.75
WISC-III VIQXVIII	0.78	-0.78	0.78	-0.78	0.78	-0.78	0.78	-0.78	0.78	-0.78	0.78	-0.78	0.78	-0.78
WISC-III VIQXIX	0.82	-0.82	0.82	-0.82	0.82	-0.82	0.82	-0.82	0.82	-0.82	0.82	-0.82	0.82	-0.82
WISC-III VIQXX	0.85	-0.85	0.85	-0.85	0.85	-0.85	0.85	-0.85	0.85	-0.85	0.85	-0.85	0.85	-0.85
WISC-III VIQXXI	0.88	-0.88	0.88	-0.88	0.88	-0.88	0.88	-0.88	0.88	-0.88	0.88	-0.88	0.88	-0.88
WISC-III VIQXXII	0.92	-0.92	0.92	-0.92	0.92	-0.92	0.92	-0.92	0.92	-0.92	0.92	-0.92	0.92	-0.92
WISC-III VIQXXIII	0.95	-0.95	0.95	-0.95	0.95	-0.95	0.95	-0.95	0.95	-0.95	0.95	-0.95	0.95	-0.95
WISC-III VIQXXIV	0.98	-0.98	0.98	-0.98	0.98	-0.98	0.98	-0.98	0.98	-0.98	0.98	-0.98	0.98	-0.98
WISC-III VIQXXV	1.00	-1.00	1.00	-1.00	1.00	-1.00	1.00	-1.00	1.00	-1.00	1.00	-1.00	1.00	-1.00

Rao V & Gupta RK et al. IJPN 2011

And these are the correlation. Memory exclusion closure they all showed some relationship in some area of the brain function on this.

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DTI correlates of cognition in term children with spastic diplegic cerebral palsy

Summary of mean DTI metrics (FA) in spastic diplegic children having low performance and normal verbal IQ (n = 8) vs low performance and low verbal IQ (n = 14)

Regions (FA)	Low performance and normal verbal IQ (Mean ± SD)	Low performance and low verbal IQ (Mean ± SD)	p
TWM	0.36 ± 0.03	0.27 ± 0.07	0.02
OWM	0.48 ± 0.06	0.40 ± 0.07	0.03

Tan T & Gupta RK et al. 2019 [11]

Now this was the question which was very interesting it was asked that there are some of the children which had a low IQ as compared to the normal verbal IQ. And he said may be it is effecting the reverse side you know where ever the f a varies. And what you found there was significant area in the brain like the temporary white matter and the oscillary white matter. It showed a significant difference in the f a was in the 2 groups also. It mean the white matter damage are more in children with the poor performance you can see that 4.48.4.0.27 as compared to the and these are involved the IQ the temporal and the oscillator are involved in the IQ as well. This was pointed out by the reviewer so we have to reanalyse the data and he said he want to look this and have a look and see what it is and we informed them of this. So I think with this I conclude that there is a defect in competition as you can see there have the relationship with the white matter relationship with the grey matter changes blood flow are there which are being affected by the CP. And the changes of plasticity are seen on the therapy.

So, it is a area which involves a neurologist and also orthopaedic surgeon psychologist psychiatrist and radiologist. So this is a very wide area which involves everybody from the point of view of the neuroscience all sector of neuroscience involved in this kind of disease process. And which can be very you know gratifying if you can help these

children little bit. In any way may be in the community improvement may be in motor improvement may be in psychological improvement whatever. So these children really deserve it and not their fault when they are born? And we can definitely make some difference little bit by whatever way it is to and there are number of societies spare societies are available in the country they do hardly anything except making money.

This the most discomfoting part of this story you know I have tried to contact number of these agencies. Because I wanted children with CP that is how I contacted with them and they said no we want this and we want that and so those kind of thing as well, I can do a human life free I cannot emotion that. So, these are the commercial organisation not really the philanthropy organisation and they are the 1 which are harming the kids rather helping them you know. They give some wheel chair this and that to make them comfortable, but what is going behind that who would know it that. So, I think it if a person in computer science is interested in this area specially we can help them by improving their you know IQ improving their by what is called psychotherapy? So, this is where the area usually you can help actually with these children

Student: With this thing I conclude I think my presentation in this it is related to one of your first presentation. You said that CP is something which does not worsen and it does not improve. Once the injury is positive then why that between 1 to 4 years of age there was actually the difference ID difference was increasing and changing between normal children.

See normally whatever demo has occurred at the early stages over so the IQ in the first 3 months were nowhere to quantify to actually whatever the daily score is there whatever the whatever you do you know you calculate that. And once you started calculating the IQ it is at the bottom where ever it is. So, what I am saying is that though the child is the normal child the IQ is up here the i q is not bothered from practically the time you start to quantifying the IQ that is what even this is from the published literature. I am saying this what is important that is how they show that and CP is also injury occurred to the brain.

The only way you can improve function is by improving the placidity by physiotherapy by whatever psychotherapy or they call it as different therapies people are now, giving to see their concretion improvement see their motor improvement. This is just a way to

improve their placidity brain has a lot of reserve. The beauty of brain is at whatever is damage is not that is all well known to the brain. You have to get the area out which is can become more functional and more active in this that is, but definition CP is it does not it does not worsen.

You will learn to find a child of grade 4 grade 2 become grade 3 no he will remain grade 2 he can become grade 1 improve if you help them with a you know all kind of things, but suddenly he will not go to grade 3. But in an ordinary disease you see like for example, tumour for example, some metabolic disorders you know like ADI this Adriatic dystrophy or something there is a constant decline as the function of age. It is a progressive disease, but this is not progressive disease whatever had to happen has happen you cannot go beyond what you are you can go only improve you cannot go down.

That is why the in fact people were saying initially all people are dying with CP as early as 1 month and 2 month and so and so forth. But if look at the literature about ten years back the definition of CP was a child has to be 2 years no progression at 2 years we call it as CP. Now, the definition is changing, because new technologies available new methods are available to save CP to show it is hypoxia we have done a study where we this show the child. See the child's birth showing hypoxia classic hypoxia we followed the way function of each that is some more you can publish actually it is hard work which was done by one of the students actually.

And he just could not publish that their study where he showed repeated studies that how the tissue is changing with age in that area. Most of the time area does not change very much it stays there actually. So, you can catch CP as the earlier 1 month or earlier 1 day rather than calling it 2 years that is how the definition is evolving. But not like 5 years we did the test we say 2 years you have to wait final definition. But that definition is not accepted in the academic community it is still accepted as text to company level, but not at the research level not accepted any more. There is another question that relates to the DTI code relation combination. Now, what are the measures of combination where you measuring the process when it was going on or if it was a test like IQ tester.

Well, it was like the kids who are available for testing different like I gave the names of the kids which we used. And those kids were done at the baseline and after 6 months of therapy.

They will basically test it was all like 1 day.

No like test better test will perform.