DOWN SYNDROME: FROM THE DOCTOR'S POINT OF VIEW

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Nomenclature History

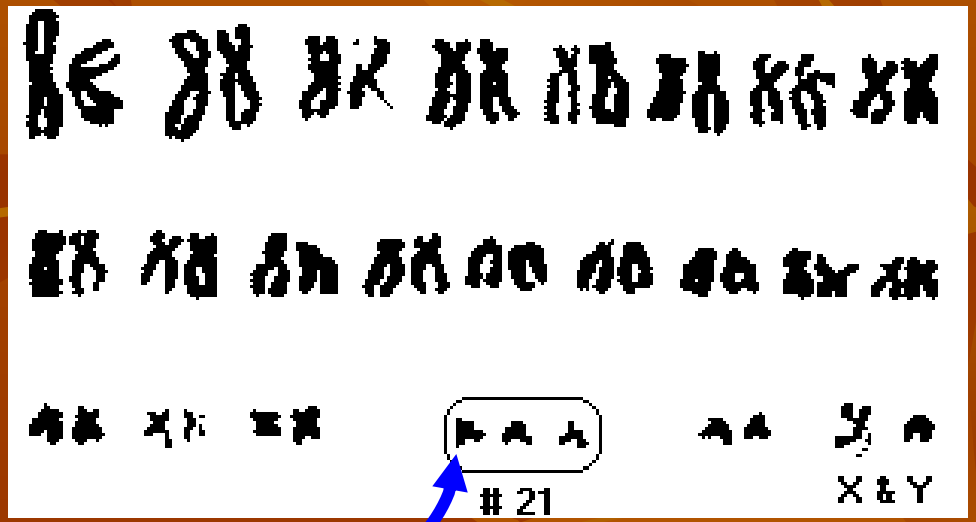
- *1866: Dr.John Langdon Down, superintendent of an asylum for children with mental retardation in Surrey, England, first described a set of children with typical common oriental features and MR whom he mistakenly called Mongoloids to distinguish them from Cretins.*
- *1960: Protests against this ethnic insult changed its name to "Down's syndrome".*
- *1970: Americans call it "Down syndrome" while Europeans continue to call it "Down's" .*

Human Genetics

- *Our genes are composed of 46 chains or chromosomes, made up of 23 chains inherited from both the father and mother (23+23=46). They combine to make 23 pairs, of which 22 are similar (Autosomes) and one pair: the Sex Chromosomes, are different: XX for females and XY for males. That also means that it is the FATHER who makes a child male or female, and not the mother.*
- *Everything about the child is written onto these chromosomes.*
- *Hence both sperms of male and ovum of the female has 23 single strands of chromosomes.*
- *After fertilization, the resulting fertilized cell has the usual 46 chromosomes, divided into 23 pairs.*

The Genetic Mistake

- *1959: Jerome Lejeune and Patricia Jacobs, working independently, first determined the cause to be trisomy (triplication) of the 21st chromosome*

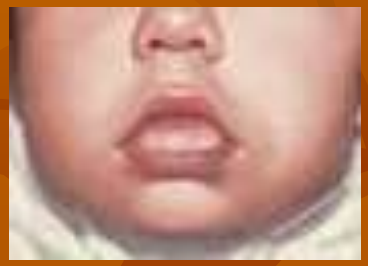


Mistake by Scientists

- *During germ cell production, occasionally the primary cell does not bifurcate fully, leaving one of the germ cells with 24 chromosomes, often involving the 21st chromosome.*
- *Recent research has shown that in these cases, approximately 90% of the abnormal cells are the eggs. The cause of the non-disjunction error isn't known, but there is definitely a connection with advancing maternal age.*

Diagnosis




- *1 in 800 to 1000 live births*
- *Mental retardation*
- *Single palmer crease (simian crease)*
- *An almond shape to the eyes caused by an epicanthic fold of the eyelid*
- *Up slanting palpebral fissures*
- *Shorter limbs*
- *Poor muscle tone*
- *Larger than normal space between the big and second toes*
- *Protruding tongue*
- *Multiple health concerns, as discussed later*

Prenatal Diagnosis

- *Ultrasound by* **experienced** *Ultrasonologist:*
  - Nuchal translucency
  - Deformity of nasal bone
  - Cardiac structures
- *Villus (fingerlike protrusions of placenta) sampling*
- *Amniocentasis (Removing fluid from uterus to test).*

- ***WARNING***:
  - Most abnormal fetuses abort
  - Prenatal diagnosis may be 90%+ correct, but not 100 %
  - Instances are on record that (+) Diagnosis was made, parents decided not to abort and went on to have a normal child.

But those who know how to do a complete Diagnosis also know what steps to take

For us lesser mortals, here is a small preview of what we all ***can*** *do.*

Down Syndrome: a genetic fait acompli. So why think of treatment?

Diabetes and Hypertension are also genetic fait accomplii"

Don't we treat them?

Incidence by Age of Pregnancy

Age (years)	Frequency of Fetuses with Down Syndrome to Normal Fetuses at 16 weeks of pregnancy	Frequency of Live Births of Babies with Down Syndrome to Normal Births
15 - 19	----	1 / 1250
20 - 24	----	1 / 1400
25 - 29	----	1 / 1100
30 - 31	----	1 / 900
32	----	1 / 750
33	1 / 420	1 / 625
34	1 / 325	1 / 500
35	1 / 250	1 / 350
36	1 / 200	1 / 275
37	1 / 150	1 / 225
38	1 / 120	1 / 175
39	1 / 100	1 / 140
40	1 / 75	1 / 100
41	1 / 60	1 / 85
42	1 / 45	1 / 65
43	1 / 35	1 / 50
44	1 / 30	1 / 40
45 and older	1 / 20	1 / 25

Do not delay child-birth. Whole life left for career

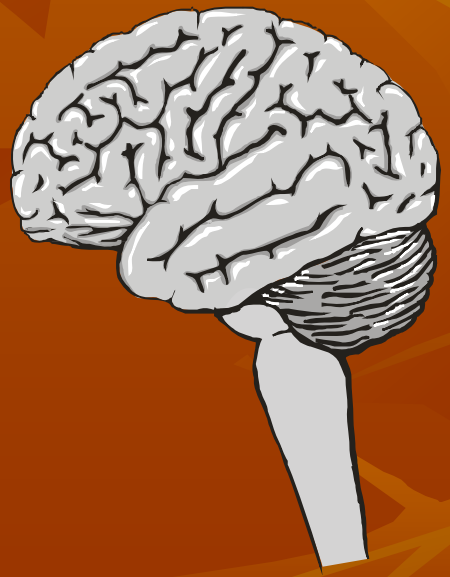
Hook EB. JAMA 249: 2034-2038, 1983.

Medical Check-up

Down's is a genetic disorder causing Mental Retardation, which cannot be improved.

So, where does a doctor fit in?

Brain (Central Nervous System or CNS)



CNS Problems

- *Epileptic Seizures: in 5 - 10%*
  - Need not be classical generalised fits.
  - Could be minor ones as seen in Cerebral Palsy.
  - Regular Therapists should keep watch and refer at once
- *Most prevalent in **infancy**, and again in **20s & 30s***

Pediatric Neurologists can offer significant help

Alzheimer's disease – What is it?

- *The human brain has a network of billions of nerve cells and connections known as synapses.*
- *They become non-functional as part of aging.*
  - **Similar to slow moving traffic when lanes on a highway are blocked**
- *Starts to manifest after the age of 65 years, but could also start earlier.*
  - **Early diagnosis important, as all mental problems must not be put under umbrella of Down Syndrome**

Alzheimer's Disease – Some Warning Signs

- *Recent memory loss or misplacing things*
- *Difficulty in performing familiar tasks or disorientation of time and place*
- *Change in mood or behaviour or personality*
- *Problems with language and abstract thinking*
- *Poor or decreased judgment and loss of initiative*

Alzheimer's Disease – Incidence in Down's

- *General population: approx 6%*
- *Adults with Down's syndrome: 25%.*
  - Many individuals with Down syndrome have the changes in the brain associated with Alzheimer's, but do not necessarily develop the clinical disorder.

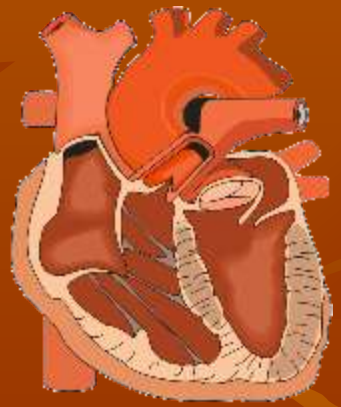
Can doctors help? Yes, to an extent

- ***Vitamin E*** *(natural is better) delays the time to clinical worsening.*
- ***Omega-3 fatty acids****, especially DHA has been found quite useful in early cases in preventing brain degeneration.*
- ***Testosterone*** *may help by protecting neurons against premature cell death.*
- ***A coctail*** *of folate, vitamin B6, alpha-tocopherol, S-adenosyl methionine, N-acetyl cysteine, and acetyl-L-carnitine, in a 12-month, open-label trial with 14 community-dwelling individuals with early-stage showed promise.*
- ***Status of HBOT*** *is un-established at this point*

Not available in India

- ***Aricept****. a cholinesterase inhibitor, may improve memory and daily living.*
- ***Namenda*** *may act by regulating glutamate in improving learning and memory.*
- ***Exelon*** *&* ***Razadyne*** *inhibit breakdown of acetylcholine*
- ***Cognex*** *inhibits cholinesterase and slows breakdown of acetylcholine.*
  - Exelon, Razadyne, and Cognex seem to help only in with mild or moderate cases.

CVS (Heart & Blood Vessels) & Blood



Cardiovascular Problems

- *Heart problems reported in 30 - 60%*
  - Abnormal heart rhythm, fainting episodes, palpitations, or chest pain **secondary to heart lesion**
  - May sometimes be correctable by surgery.
  - Recommended time is within 1st 6 six months.

Congenital Heart Disease

- *Can occur in 40-50%; often seen in hospitalized cases (62%)*
- *Common cause of death in first 2 years of life*
- *Types:*
  - Endocardial cushion defect (43%)
  - Ventricular septal defect (32%)
  - Secundum atrial septal defect (10%)
  - Tetralogy of Fallot (6%)
  - Isolated patent ductus arteriosus (4%)
- *About 30% of patients have several cardiac defects*
  - Most common: PDA (16%) & Pulmonic Stenosis (9%)
  - About 70% of all endocardial cushion defects associated with Down
    - *www.emedicine.com/ped/topic615.htm last accessed 24 Jan 2008*

surgery often, but not always possible

Immune System

Keeping us alive against all odds

Immune system

- *Disturbed immunity is common*
- *Recurrent respiratory and systemic infections*
  - 12-fold increased risk of infectious diseases, especially pneumonia, because of impaired cellular immunity
    - *www.emedicine.com/ped/topic615.htm last accessed 24 Jan 2008*

Leukemia - 1

- *Relative risk of acute leukemia in the first 5 years of life is 56 times that of individuals without Down syndrome.*
- *Approx. 1 in 150 patients develops leukemia.*
- *CAUTION: Neonatal leukemoid reactions (ie, pseudoleukemia) are common, and distinguishing this from true leukemia frequently poses a diagnostic challenge.*
  - *www.emedicine.com/ped/topic615.htm last accessed 24 Jan 2008*

Leukaemia - 2

- *Most cases: Acute megakaryoblastic leukaemia*
  - 1st three years of life
  - Properly managed, it has a good prognosis
  - Another form of leukaemia also seen in new-borns with Down syndrome, that disappears spontaneously during the first 2 to 3 months of life.

Musculo-Skeletal Systems

Spinal Deformities – Atlanto-Axial Instability (AAI)

- *Found in approximately 14% of Down's*
  - Increased mobility at level of 1st & 2nd vertebrae ➔ compression of the spinal cord.
    - *Neck pain*
    - *Loss of upper body strength*
    - *Changes in bladder and bowel functioning*
    - *Changes in gait and unusual posturing of the head & neck.*
  - Majority of the 14% will be asymptomatic
  - About 10% (= 1% of Down's) likely to experience problems, esp. if involved in sporting activities.

Physical Abnormalities - 1

- *Short arms and legs*
  - More difficult to learn sitting because they cannot lean forward and use their arms to prop them up
  - When falling, they fall further before being able to catch themselves
  - Climbing more difficult due to short legs
  - Usually learn to walk at 24 months rather than at the average 12 months.

Physical Abnormalities - 2

- *Decreased muscle strength*
  - Child locking their knee when standing.
- *Hypotonia, esp. hips, making it harder for child to balance.*
  - Diminishes over time but will persist throughout life
  - Compensatory but abnormal postures and stance
- ***Hence need for DAILY Expert Occupational Therapy***

Dental Problems

- *Teeth usually come through late and in an unusual order.*
- *Some teeth can be missing and those that are present can be small and misshapen.*
- *Because the mouth is small crowding can occur.*
- *Problems with gingivitis and periodontal disease.*
- **Yearly Dental Check-up & Management**

Other Systems

Abdominal / Genito-Urinary Disease

- *Gastro-Intestinal System (12%):*
  - Duodenal atresia or stenosis, Hirschsprung disease (<1%), fistula, Meckel diverticulum, imperforate anus, umbilical hernia, etc.
  - Celiac Disease in 5-15%
- *Genitourinary tract:*
  - Renal malformations, hypospadias, micropenis, and cryptorchidism occur.
    - *www.emedicine.com/ped/topic615.htm last accessed 24 Jan 2008*

Corrective surgery possible in many cases

EYE & ENT Problems

- *Eyes:*
  - Congenital cataracts → blindness if not treated early.
  - Blepharitis, Conjunctivitis → medically manageable
- *ENT:*
  - Obstructed airways leading to snoring, unusual sleeping problems and sinusitis → medically manageable
  - **Hearing Loss is a significant concern**
    - *For some the loss may not occur until their teens leading to misdiagnosed behavioural disturbances → medically manageable.*

Endocrine Problems

- *Thyroid problems significantly increased, affecting growth and cognitive functioning.*
- *Thyroid Function blood tests and appropriate therapy can offer significant help*

Management

Where do we start?

Standard Recommendation: 1-5 yrs

S N Van Cleve; J Ped. Health Care; 2005; 20(1): 47-54

- ***Assess problems with eating:*** swallowing / allergy
- ***Manage constipation:*** dietary fibres/polyethymene glycol
- ***Sleep Disturbance:*** correct sleep apnea / URT obstruction
- ***ENT:*** Look for serous Otitis media → hearing loss

Standard Recommendation: 1-5 yrs

S N Van Cleve; J Ped. Health Care; 2005; 20(1): 47-54

- ***Neuro-Developmental Progress:*** Regular assessment and planned target oriented Standard Therapy (OT + PT + Special Education + Sensory Integration + Speech Therapy)
- ***Social / Behavior Adjustment:*** Counseling of child / family to help integrate him into family & society
- ***Yearly Follow Up:*** TSH, Hearing, Eye, Dental, Ortho

Standard Recommendation: 5-12 yrs

S N Van Cleve; J Ped. Health Care; 2005; 20(1): 47-54

- ***Yearly Assessment:*** TSH, Physical Growth, Dental, School progress, Standard Therapies
- ***Psycho-sexual development****, acceptance of some responsibilities in family and society*
- ***Balanced diet***
- *Start planning for* ***supportive care***
- *Continue* ***Standard Therapy***

Don’t neglect the Doctor’s responsibilities

- *Pregnancy counseling (don’t delay!!!!!)*
- *Watch for seizures, early signs of Alzheimer's or Thyroid abnormalities*
- *Rule out Cardiac disorders, especially congenital defects*
- *Guard against infections, leukemia due to immune abnormalities*
- *Look for spinal, dental, limb, Eye/ENT, GIT and GU developmental defects.*

Physical therapy

- *These children will walk at 24 months even without OT/PT*
- ***Early** OT/PT can help avoid abnormal compensatory postures / gait / stance*
- *Untreated, these can significantly impair adult QOL*

Speech and Language therapy

- *High risk of developing speech and language problems*
- ***Hearing defects can be a factor***
  - Can also arise from poor development of muscles of speech production, large tongue & small oral cavity.
  - Therapist should focus on exercising the muscles of speech production as well as focussing on memory and understanding.

Modern High Funda

- *For long considered just a genetic disorder, where nothing can be done to improve CNS function.*
- ***In desperation**, some experimental avenues are being investigated*
- **WARNING: EXPERIMENTAL AVENUES**

MTHFR

- ***Methylene Tetra Hydro Folate Reductase*** *is an enzyme that methylates Tetrahydrofolate, which converts ordinary B12 to Methylcobalamin, which converts Homocysteine to Methionine.*
- *Methionine penetrates brain to donate the "Methyl" part for intra-neural signaling by DNA and RNA, while the remnant goes on to form Glutathione, the sole scavenging agent or brain cells.*
- *MTHFR deficiency leads to abnormal brain function as well as Glutathione deficiency which reduces body's Free radical Scavenging activity as well as detoxifying capacity of brain cells.*
- ***MTHFR deficiency is seen in Autism, & also in Down children***

MB12 Supplementation

- *MB12 absorbed by specific intestinal mechanism which uses intrinsic factor and by a diffusion process in which approximately* ***1% of the ingested dose is absorbed****.* ***Its Bl. Level is erratic***
- *In ASD,* ***only*** *MB12 25 mg/ml given by S/c route in gluteal fat maintains the flat blood level necessary to achieve optimum CNS activity.*
- ***Do we do the same for Down… only time will tell. This research has not been started.***

CT-cum-SPECT FUSION Scan of Brain

- *This is one of the latest means of assessing Functional Component of Brain*
- *Can show which areas of brain are getting and using perfused nutrition / oxygen, thereby signifying a corresponding degree of activity*
- *In Children, mostly done in* **CP**, *later* **Autism Spectrum Disorder** *& now just beginning to be done in* **Down Syndrome**

Example of a CT-cum-SPECT Fusion Scan of Brain in CP

Code used

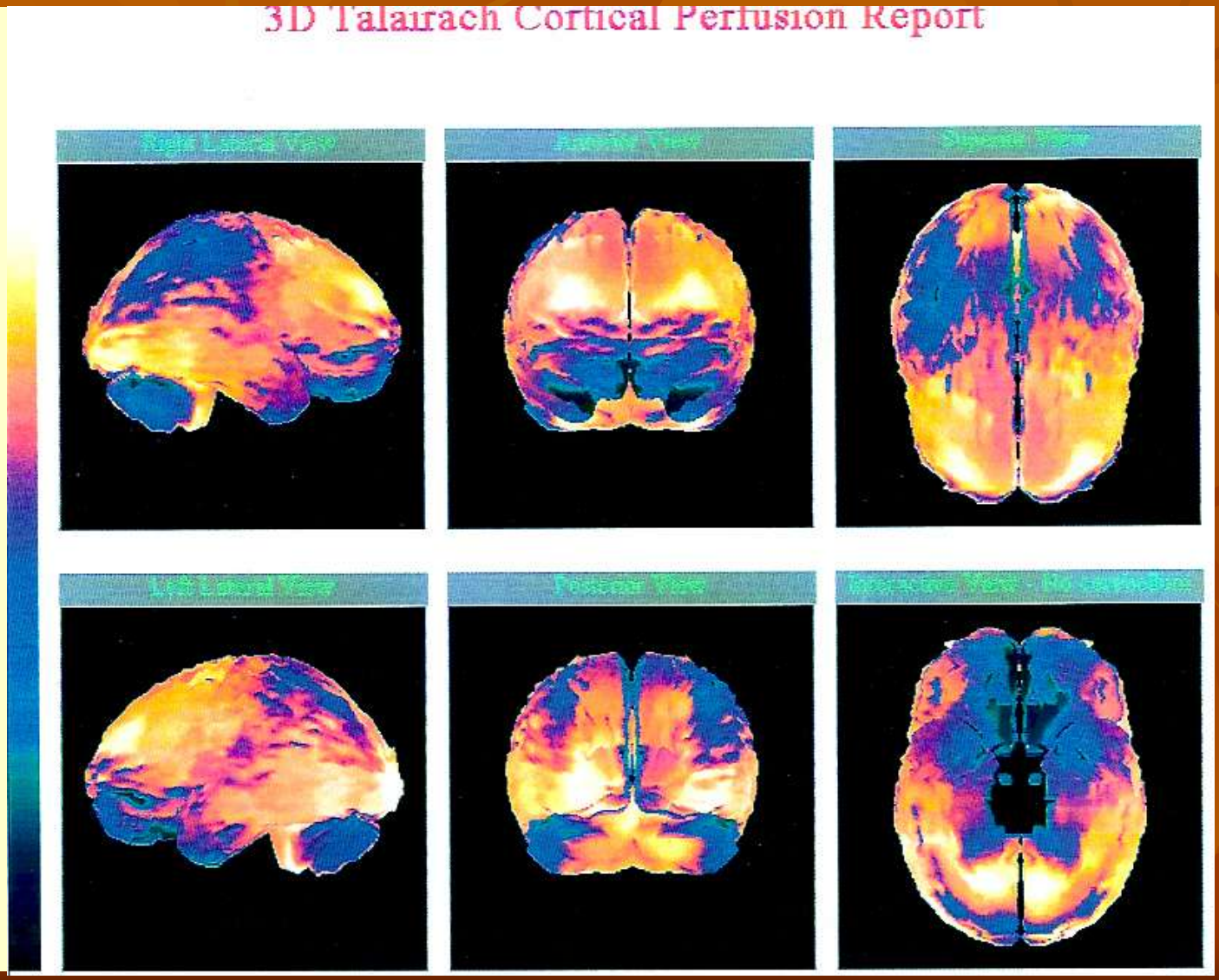
Active normal

Inactive normal

Reduced perfusion

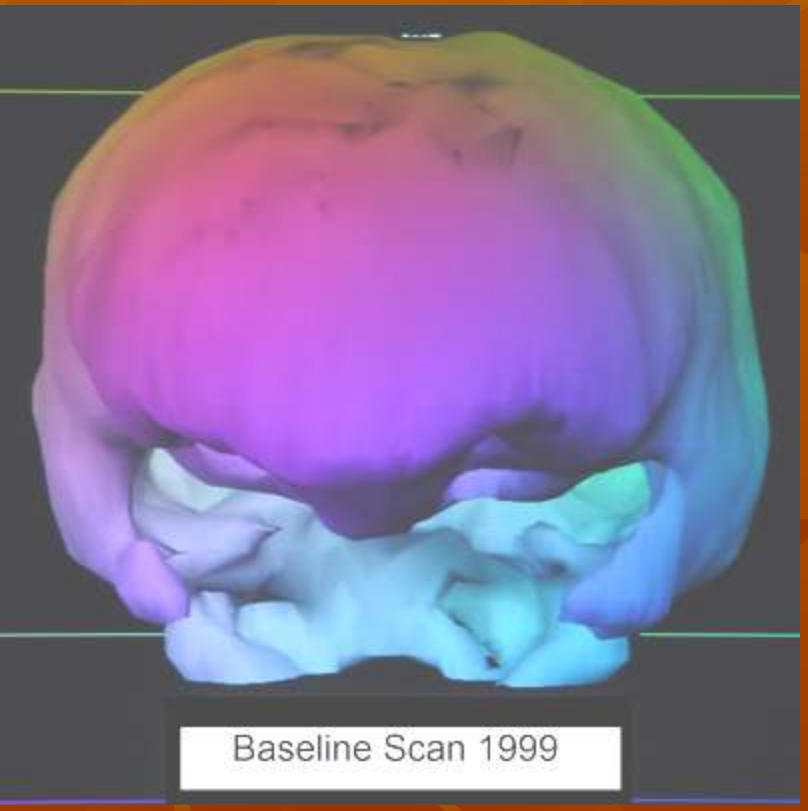
Severe anoxia

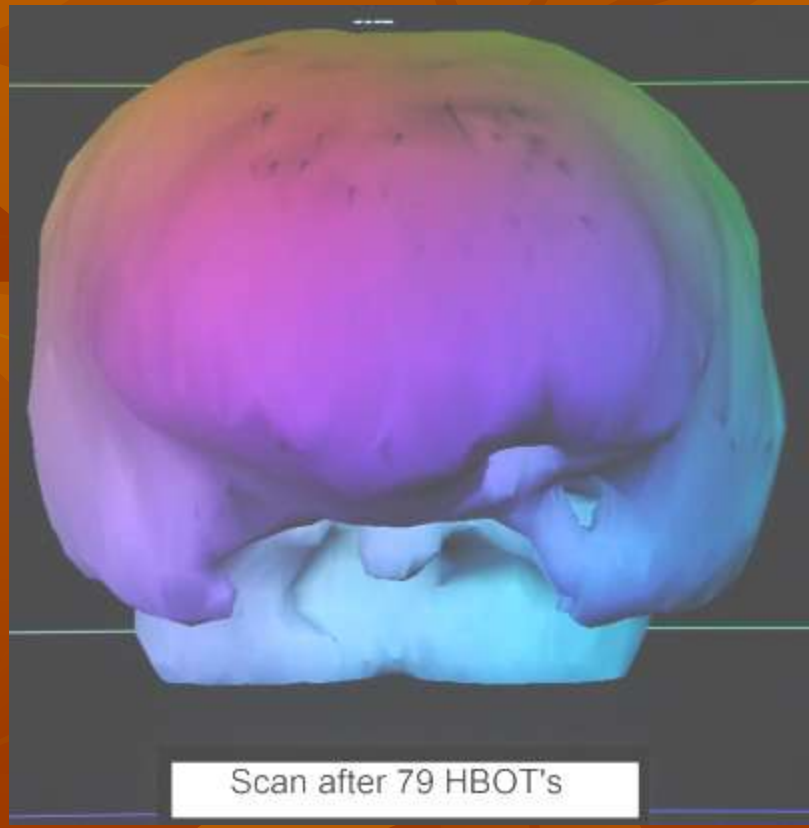
Practically no perfusion



Courtesy UDAAN

Example of similar SPECT Fusion Scan of Brain in ASD *(Courtesy Dr. Paul Harch)*





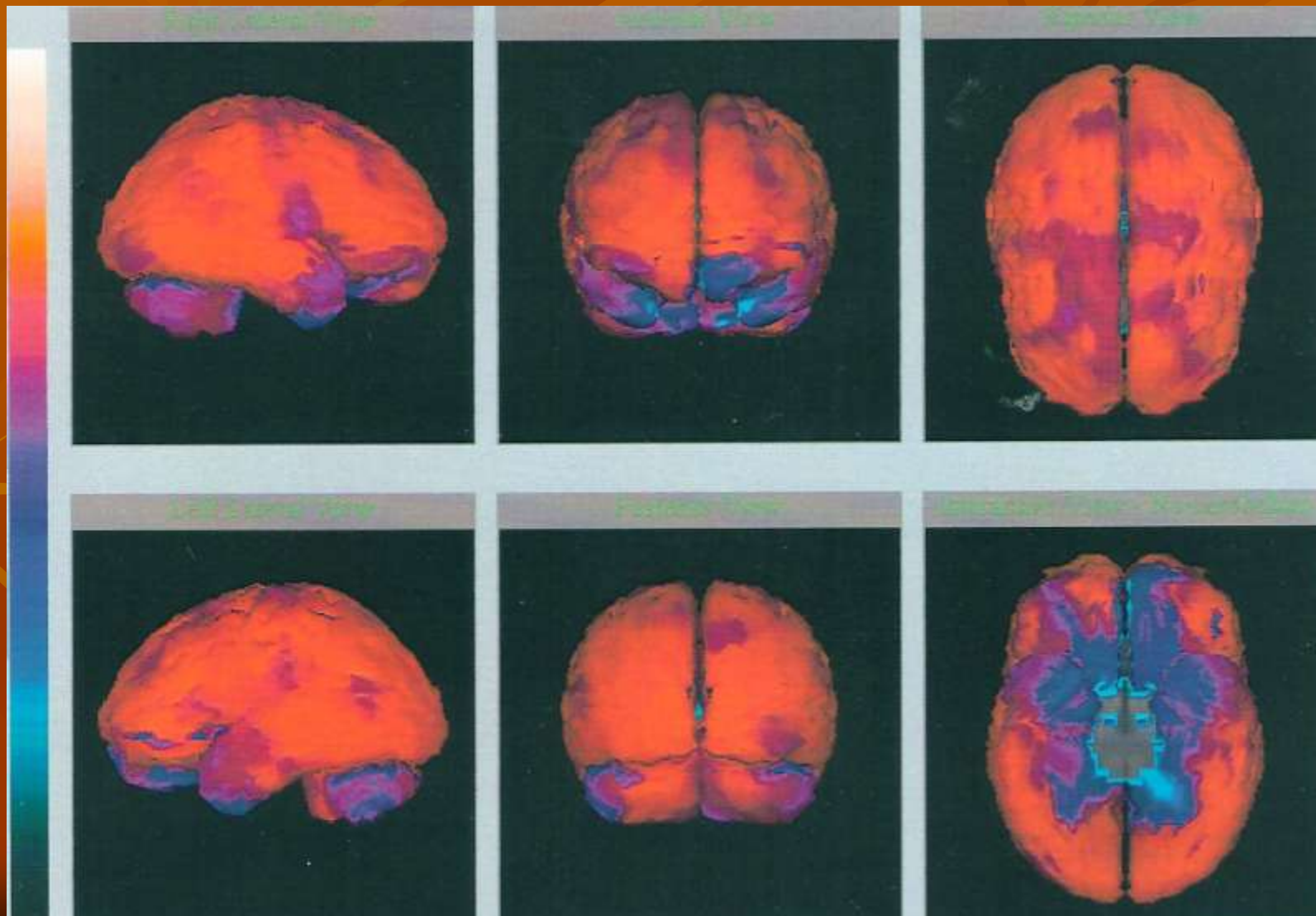
Color Code Used: Purple area represents NORMAL Brain tissue, damaged area translucent

Pre- and Post HBOT MRI-SPECT Fusion SPECT scan showing repair and re-growth of neural tissue in frontal lobe following HBOT

Example of SPECT in Down 3-D External View showing Anoxia

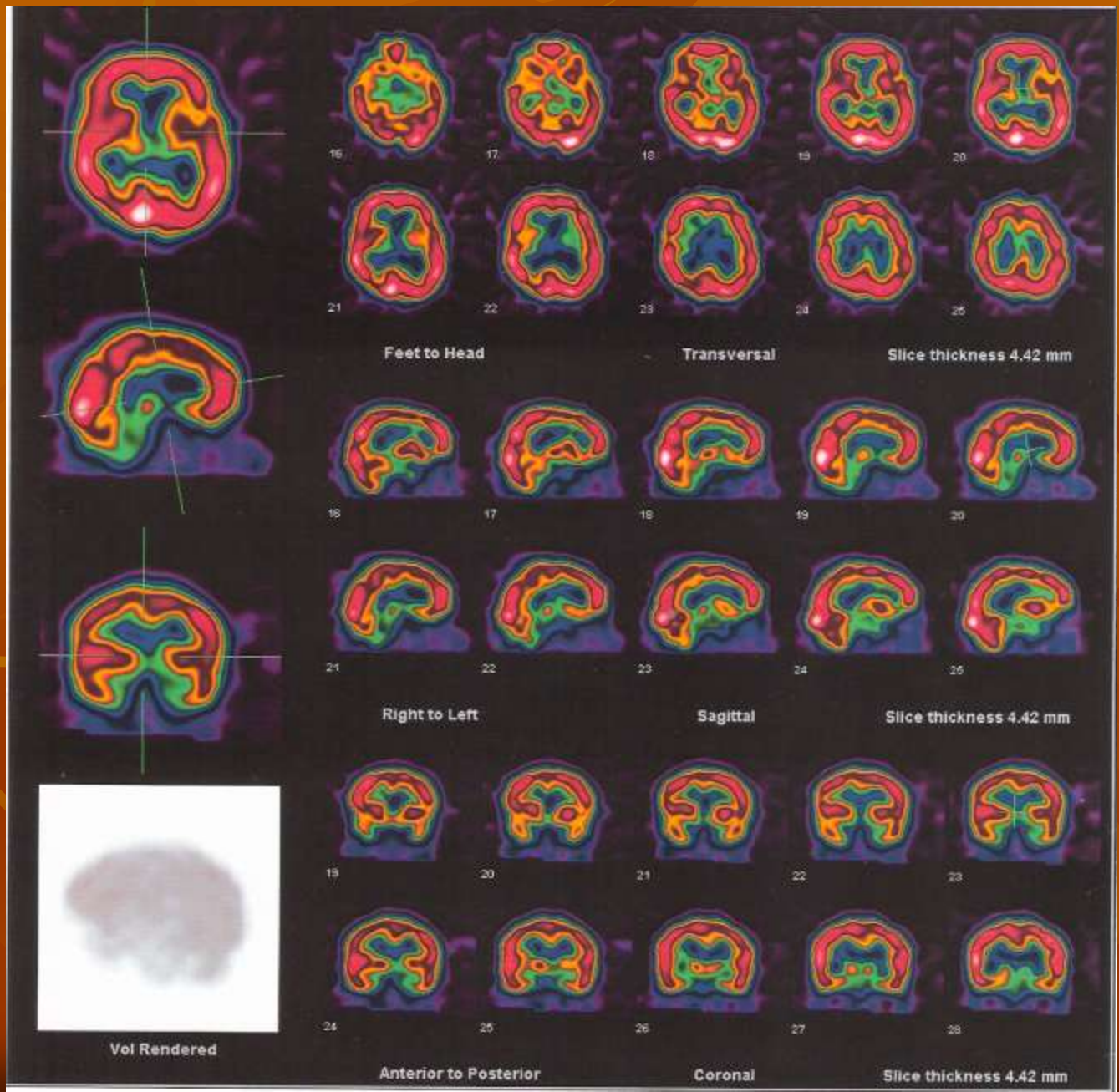
This is one of our kids.

He is scheduled to start getting **experimental** HBOT next month: the 1st such case in Asia, barring maybe China.



3-Axis Cross Sectional View

This is one of our kids.



Compare the three

- ***Notice the similarity?***
  - Maximum perfusion defect in CP
  - Moderate perfusion defect in ASD
  - Noticeable perfusion defect in Down also
- ***Experimental research*** *is underway using HBOT in Down.*

  Too early to predict long term benefit though short term benefits are already available as per Net Search

What is HBOT?

- *Hyperbaric Oxygen Therapy is a process to provide Oxygen to a patient kept at higher than normal atmospheric pressure inside a pressure chamber.*
- *The pressure increases the solubility of oxygen in blood plasma and tissue fluid (Henry's law) to enhance availability of oxygen to anoxic tissues all over the body.*

So where do we go from there?

- ***It is a very difficult question.***
- *Very early, **ANECDOTAL** data suggest that **Down cases with anoxic damage in brain** may show a satisfactory outcome with the use of HBOT, but we still have not established how much and how often to give. **It is still experimental**.*

- ***For lack of time, we will discuss HBOT on some other occasion**.*

Thanks for your patient hearing