Genetic issues in cerebral palsy: the Bradford experience

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Genetic issues in cerebral palsy: the Bradford experience

- Background to our experience of genetic conditions
- Cerebral palsy in Bradford (1997 report)
- Review of genetic factors in cerebral palsy

Bradford

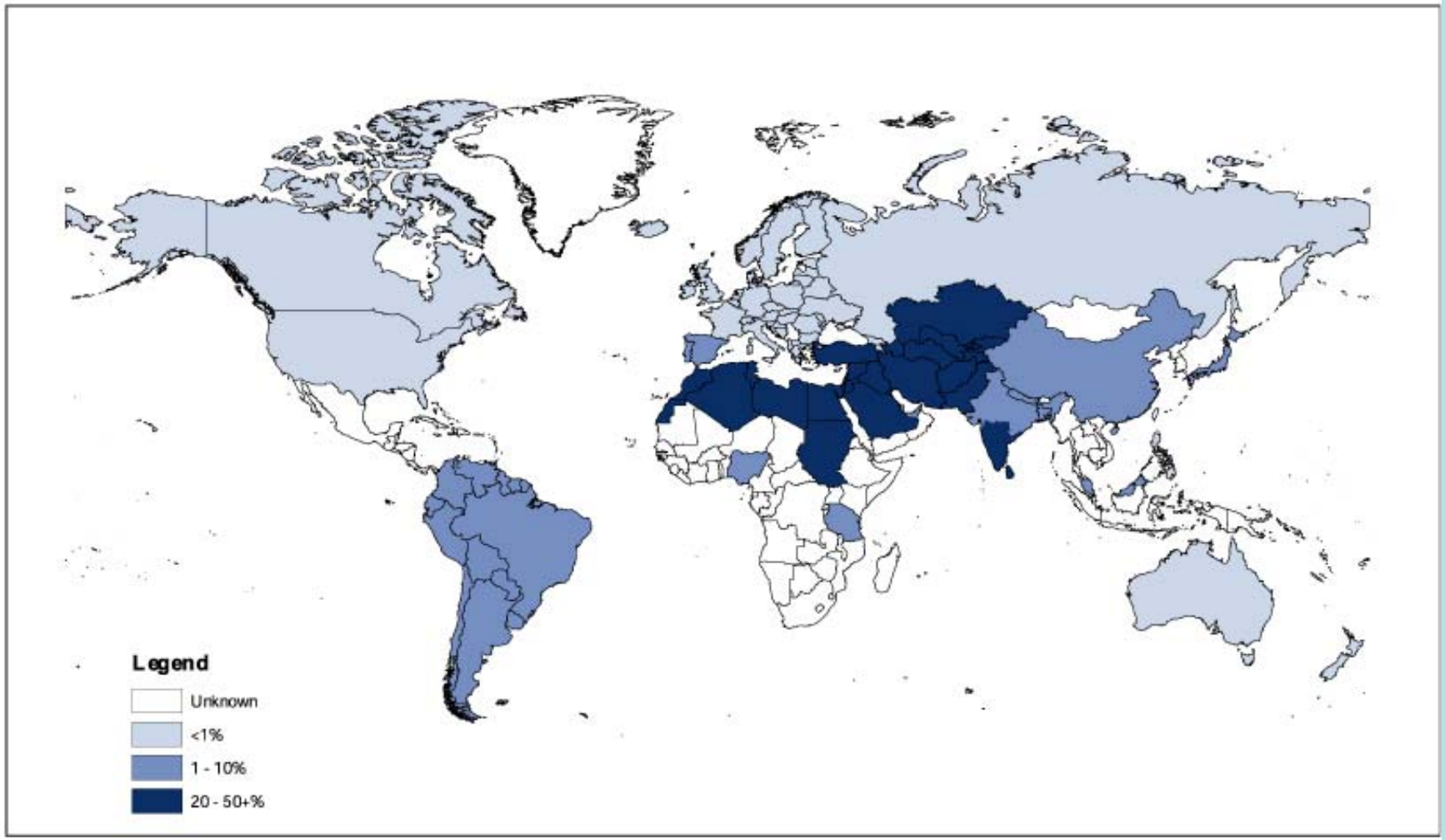
- Population c360,000
- Children (up to 18) c106,000
- Annual births 5,000-6,000
- Pakistani origin births >45%
- Consanguinity in Pakistanis 70-80%

- These figures exclude Airedale

Cousins and clans

- Consanguinity: marriage within the family, occasional in western societies (but more popular in royal families)
- Endogamy: marriage within the community, popular in certain groups (e.g. Amish, Irish Travellers) and used to be very common with limited travel options
- Both very common globally

The global distribution of consanguineous marriage



Cousins and clans

- First cousin marriage is most popular
- Some are double first cousins (i.e. your partner's mother and father are both blood relatives)
- Even if not cousins, many marriages are within the biraderi or clan. These may show a founder effect (c.f. Amish)

Risk of having a child with disability

- Unrelated parents 2-3%
- First cousins 4-5%
- Double first cousins 6-7%

- BUT also increased with maternal age, smoking, drinking, drugs, poor nutrition, poor obstetric/healthcare

Risk of having a child with disability

- Risk for first cousins is still low (i.e. 4% instead of 2%, 96% have healthy children) but this is doubled, not a 2% increase

- Risk for the community is an extra 2% incidence (i.e. with 2,000 consanguineous births each year, an extra 40 children with autosomal recessive [AR] conditions)

Added risks - community customs

- Child of random first cousins has risk that 6% (1/16) of genes are homozygous

- Child of first cousins from UK communities preferring consanguinity has risk that 11% of genes are homozygous

Woods C G, 2006 (Am J Hum Genet)

Down’s syndrome

- Maternal age 20 1 in 1724
- Maternal age 35 1 in 365
- Maternal age 40 1 in 109

Hook and Chambers 1977

Impact in Bradford

- Neurodegenerative conditions
- Microcephaly
- Deafness
- Neuromuscular conditions
- Rare genetic conditions

- 144 AR conditions across paediatrics

Conditions at my clinics recently

- Aicardi-Goutières syndrome
- Aspartylglucosaminuria
- Berardinelli-Seip congenital lipodystrophy
- Brown-Vialetto-van Laere syndrome
- Fraser’s syndrome
- Hyperekplexia
- Joubert syndrome

Neurodegenerative conditions

- Progressive Intellectual and Neurological Deterioration (BPSU study)
- 798 UK children
- 50 in Bradford
- 27 different conditions identified in larger local study, mostly autosomal recessive

Devereux G, 2004 Arch Dis Child

Positives

- Clinical series - juvenile Sandhoff disease
- Genes for Aicardi-Goutières syndrome
- Trials of potential treatments
- Lottery funding for community paediatric palliative care (but under threat)

Microcephaly

- 44 children
- 35 congenital, 9 postnatal
- Congenital:
- 27 Pakistani
- 7 Caucasian
- 1 Bangladeshi

Corry P, 2002 Community Genet.

Positives

- Geneticists have identified 6 gene loci for Primary Microcephaly
- Better understanding of what these genes do, and how the human brain grows

- Channel 4. “What makes us human”? on August 12th, 19th.

Roberts E, 2002 (J Med Genet)

Deafness

- Prevalence in Bradford (1995)
  - Asian children 4.69 / 1,000
    - Genetic cause 2.41 / 1,000
    - Unknown cause 1.52 / 1,000
  - Non-Asian 1.38 / 1,000
    - Genetic cause 0.36 / 1,000
    - Unknown cause 0.54 / 1,000

Parry G, 1996 Univ of Manchester MSc thesis

Positives

- Early work on connexin gene
- One of first sites for universal neonatal screening
- Elizabeth Foundation centre for North of England

Campbell D A, 1997 J Med Genet

What does all this have to do with Cerebral Palsy?

Cerebral Palsy

"A persistent, but not unchanging, disorder of movement and posture due to non-progressive disorder of the immature brain".

Brett E M

In Paediatric Neurology 1983

Causes of cerebral palsy

- Media – poor care in labour room?
- Reality – only 10-15% due to problems during labour and many unpreventable
- Prenatal, perinatal and postnatal
- Genetic causes – thought to be about 2%
- Increased awareness of factors in first and second trimesters, some of them genetic

Cerebral Palsy in Bradford

- Births in Bradford 1985-1987
- Using Yorkshire Cerebral Palsy register, birth records, CDC notes and clinical examination by 1 researcher
- 75 children reported to register, but 3 could not be traced, 2 refused consent and in 2 the diagnosis was changed.
- 68 children in study

Ethnicity for children with C P

- Asian children
- Cerebral palsy 29 children

  Prevalence 5.48 / 1,000

- Non-Asian children
- Cerebral palsy 39 children

  Prevalence 3.18 / 1,000

Sinha G, 1997. Dev Med Child Neuro

Asian children with C P

29 children

6 had sibling with same type of C P

1 had cousin with same type of C P

1 had aunt with same type of C P

1 had sibling with “motor impairment” but not available for examination

Cautions

- Unsophisticated ethnic data, but 26 out of 29 Asian children were Pakistani
- Data on consanguinity was vague. For Bradford Pakistanis thought to be 75-80%
- More knowledge now about marriage within biraderi / clan
- What about social factors, maternal health, language, access to maternity care?

Criticism

- It was suggested that we were wrong to concentrate on genetic factors
- What about poor obstetric care for Asian mothers?

- Apgar scores for my patients with C P were actually higher for Asian children

Turkey

- 117 children with cerebral palsy
- 352 case controls
- C P: 41 children (35%) consanguineous

  odds ratio 3.2 (CI 1.8-5.5)

  19 children (16%) with CP relative

Tüzün E H, Eker L

Presentation at EMCPDM Congress, Istanbul, April 2002

Saudi Arabia

- 103 children with cerebral palsy
- 103 controls
- Major risk factors: consanguinity, history of cerebral palsy in sibling
- Consanguinity odds ratio 2.31
- Affected sibling odds ratio 14.52

Al-Rajeh S, et al. 1991. DMCN

West Sweden (1)

- Recent mathematical analysis of prenatal and perinatal risk factors was applied to 681 children with cerebral palsy born in 1959-1970.
- Estimates that 40% of ***etiologically undiagnosed*** cerebral palsy is genetically caused.

West Sweden (2)

Estimates for genetic causes

- Premature spastic diplegia 32%
- Mature spastic diplegia 45%
- Mature hemiplegia 60%
- Pure ataxia virtually all

Costeff H, 2004

Hagberg B, Hagberg G, Olow I, 1975

Genetic causes for CP?

- Gene locus for ataxic cerebral palsy in Bradford Pakistani family mapped to chromosome 9p12-q12.

McHale D P, 2000 Eur J Human Genet

Genetic causes for CP?

- Gene locus for symmetrical spastic cerebral palsy in 3 UK families mapped to chromosome 2q24-q25.

McHale D P, 1999 Am J Hum Genet

Possible mechanisms

- Thrombophilia
- Neuronal migration disorders
- Familial porencephaly

Is cerebral palsy the right diagnosis?

- Caution:
  - Neurodegenerative disorders
  - Metabolic conditions

Gupta R Appleton R E, 2001 Arch Dis Child

Conclusions

- There is likely to be more evidence for genetic factors in causation
- Some communities have higher likelihood of genetic causes for cerebral palsy
- Resources and research need to be targeted appropriately