Abstract:

The practice of medicine is rooted in secure statistical support, derived from carefully constructed studies, to provide the knowledge base on which clinical decisions rest. In such a well-structured culture, weak disease associations or observations in small groups of patients not reaching statistical significance, whilst discrediting, are often sidelined pending further evidence. Worse, they may be considered as irrelevant observations of arraigne groups not altogether relevant to mainstream medical practice. For many doctors, Valproate Embryopathy remains just a sideshow in print. However, a recent study in the New England Journal of Medicine ushered an end to the era when the evidence for an association between Valproate exposure in pregnancy and fetal malformations might be intellectually consigned to not proven and politely ignored.

Jentink et al reviewed the extant data of malformations in offspring of Valproate exposed pregnancies and identified 14 malformations more common among the offspring of those pregnancies, though, in most cases, not reaching statistical significance. Then, using European Surveillance of Congenital Anomaly (EUROCAT) data, they performed a well-controlled study on these 14 malformations comparing the children exposed to Valproate to another group in whom no antiepileptic drug was prescribed. Valproate exposed pregnancies versus malformations never recorded with Valproate and a sex and ethnic control group consisting of infants with chromosomal abnormalities. The dataset analysed related to 80000 pregnancies in Europe between 1975 and 2005. The results showed that an overall increase in the occurrence of 2 to 3% in control populations should be anticipated among epileptic women, which was probably the major avoidable source of teratogenic agents at present.

Unfortunately the effects of Valproate also extend to intellectual and neurological deficiencies of study type or numbers of cases reported. Optimal practice is best served by mutual respect between different subspecialties and an awareness of the difficulties that arise in establishing a likely causal relationship between Valproate specifically and to antiepileptic agents generally. Moreover, with the exception of craniofacial disorders, exposure to Valproate significantly increased the risk of the other 5 malformations when compared to the outcome of pregnancies treated with other anti-epileptic agents.

This latest study adds to a growing awareness of the dangers of prescribing any antiepileptic agents during pregnancy and of Valproate in particular. It follows recent recommendations from the American Academy of Neurology that Valproate be avoided in general terms, in pregnancy owing to the increased risk of major congenital malformations. Moreover it consolidates data from previous smaller studies which suggested a likely association between Valproate, used alone or in polytherapy, but whose datasets were considered too small and therefore open to bias.

Sodium Valproate was first licensed for monotherapy in the UK in 1974. The subsequent history of how Valproate has been regarded in respect of safety in pregnancy varies for interesting study and exemplifies how difficult it can be for rare conditions to gain mainstream acceptance in medicine. As early as 1981 a possible association with neural tube defects was flagged by the report of Gomes et al., observing a lumbosacral meningocele in the offspring of an epileptic mother treated with Valproate, Clonazepam and Phenobarbital. However much greater substance was lent to this observation by the work of Bjerkedal and colleagues who estimated an odds ratio of 22.6 with regard to the likelihood of Valproate causing neural tube defects. Important changes in clinical practice were recommended, such as offering prenatal counselling to women on Valproate and, following a Lancet Editorial, that women at risk might be offered amniocentesis in an attempt to screen the pregnancy for this major malformation. Writing in 1985, Clayton-Smith and Donnai pointed out that many of the cases of spina bifida in Valproate exposed infants were unrecognised and, consequently maternal blood sample to look for raised alphafeto protein (AFP), which would usually be expected to be elevated in open spina bifida and was used as a screening test for Spina Bifida would be normal. They made the important practical point that maternal screening should be by detailed ultrasound, which is now almost universally the case.

In parallel with these developments, publications by Di Liberti et al. and Winter et al. warned of wider consequences for the fetus from Valproate exposure, and in 1991 Silver and colleagues introduced the term "Fetal Valproate Syndrome" to describe the facial features among exposed children. Epicanthic folds connecting with an infraorbital groove, shallow philtrum, small mouth, and thin upper lip were recorded by these authors among their cases. However, these findings related to fewer than a dozen cases and, while accepted by the clinical genetics community, did not gain a wider acceptance at that stage. Subsequently, many other malformations, such as tracheomalacia and lusoria, have been recorded in association with Fetal Valproate Syndrome, a diagnosis which is now widely accepted in paediatric practice.

Nongeneticists reading this may be interested to note the perspective on the treatment of epilepsy in pregnancy advanced in 1998 by Professor Sir Peter Hart on whose expertise is largely in the area of clinical genetics. He offered the view that the recent increase in the incidence of malformations of 6-7% as opposed to 2-3% in control populations should be anticipated among epileptic women, which was directly attributable to treatment than to the epilepsy per se. He went on to state that before embarking on child bearing, there should be a reassessment of the need for therapy and, if possible, a trial period on no drugs or a minimal one if necessary. Neurologists may protest that this is unnecessary, but they do not generally consider the resulting problems; the authors personal view is that this is probably the most avoidable source of teratogenic agents at present.

Unfortunately the effects of Valproate also extend to intellectual and neurological development. Mental retardation was a feature of several of the earliest cases recorded and this has been a sustained observation in subsequent reports. Moore et al. recorded learning difficulties in 23 of 34 children exposed to Valproate monotherapy and behavioural problems in 29 of the 34. Among these behavioural problems identified, these authors listed "autism." While it is fair to suggest that a link with autism has not been widely reported to date, however, it is suggested that the greatest concern about cognitive dysfunction is for children exposed in utero to Valproic Acid. Recent preliminary evidence by way of the studies of neurodevelopmental outcome at age 3 years in a prospective, multicentres study of infants born to mothers taking a single antiepileptic agent in pregnancy showed that children exposed to Valproate had significantly lower scores than those whose exposure had been to other anti-epileptic agents. It would appear that the reassuring evidence now confirms the observation of early pioneers in the field whose concerns did not then find mainstream acceptance on the grounds of deficiencies of study type or numbers of cases reported.

The mainstream practice of medicine needs to be strong in the face of ill-defined half-baked observation, popular rumour, medical faddism and profit driven propaganda. Practice must not be scientific or dismissive of uncomfortable findings, even if individually rare. Optimal practice is best served by mutual respect between different subspecialities and an awareness of the difficulties that attend consolidating rare events in medicine by the rules of statistical analysis. Fetal Valproate syndrome is a good example of the consolidated course which a rare condition may take to emerge into mainstream acceptance. It behooves all who
prescribe Valproate to be aware of potential offspring consequences for female patients in the reproductive age range. Recent evidence suggests that the focus in respect of latter day prescribing of Sodium Valproate may have shifted from Neurologists towards Psychiatric practice, where its use as a mood stabiliser makes it the most commonly prescribed agent for young women. An unresolved issue remains in respect of embracing the concerns of those in medicine whose expertise in rare disorders places them outside the mainstream voice and therefore at risk of being unheard. The question is whether it should take 30 years for the teratogenic effects of a commonly prescribed drug to be accepted and mainstream practice modified.

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References

Comments:

Rare but Real - The Effects of Sodium Valproate in Pregnancy