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The link between migraine and the heart: update on recent research and progress on the MIST Trial

Introduction

Last year in Issue 10 we published a newsletter investigating the link between migraine and the heart, specifically the association between the patent foramen ovale (PFO) and patients having migraine with aura. To summarise, studies in patients being evaluated or treated for PFOs or other right-to-left shunts indicate a prevalence of migraine (particularly migraine with aura) that is several-fold higher than values expected for the general population. Small retrospective studies of patients with stroke or decompression sickness whose PFOs were percutaneously closed serendipitously showed concomitant resolution or improvement of co-morbid migraine. The postulated mechanism for this effect is that PFOs permit paradoxical microemboli and/or vasoactive chemicals in the venous circulation to bypass lung filtration, travel to the brain and trigger migraine attacks.[1] The vasoactive agent could be an amino acid, a steroid or a prostaglandin.[2]

The MIST (Migraine Intervention with STARFlex® Technology [NMT Medical Inc, USA]) Trial was designed to investigate these retrospective data in a large randomised, double-blind, placebo-controlled trial. The MIST Trial was designed to investigate whether PFO closure using the STARFlex® Septal Repair Implant is an effective treatment for patients with refractory migraine headache. Epidemiological data on the prevalence and type of right-to-left shunts in patients having migraine with aura could also be ascertained.

This MIPCA (www.mipca.org.uk) newsletter updates MIPCA members on recently published data on the relationship between migraine with aura and PFOs, and presents initial epidemiological data from the MIST Trial.

Inheritance of PFOs and migraine with aura

A blinded study determined whether atrial shunts (large PFOs and small atrial septal defects [ASD]) are inherited and whether this has a role in the inheritance of migraine with aura.[3] Atrial shunts were detected by contrast echocardiography in 71 relatives of 20 probands with a significantly sized atrial shunt (large PFO or ASD). Results showed that the occurrence of atrial shunts was consistent with autosomal dominant inheritance. When the proband had migraine with aura and an atrial shunt, 15 of the 21 (71.4%) first degree relatives with a significant right-to-left shunt also had migraine with aura compared with three of 14 (21.4%) without a significant shunt ($p < 0.02$). In conclusion, there is dominant inheritance of atrial shunts, which is linked to inheritance of migraine with aura in some families.

Relationship between size of shunts and migraine

A review of published studies showed that the prevalence of migraine with aura increased with the size of the right-to-left shunt, from 4% with small shunts to 25% with medium and 53% with large shunts (Figure 1).[4]

Effect of PFO closure on migraine attacks

PFO closure by transcatheter and surgical procedures has been used to treat cryptogenic stroke, transient ischaemic attacks (TIAs) and sometimes decompression sickness in divers. Recent *post hoc* analyses of the results of these studies have investigated the effect of PFO closure on co-morbid migraine (Table 1).

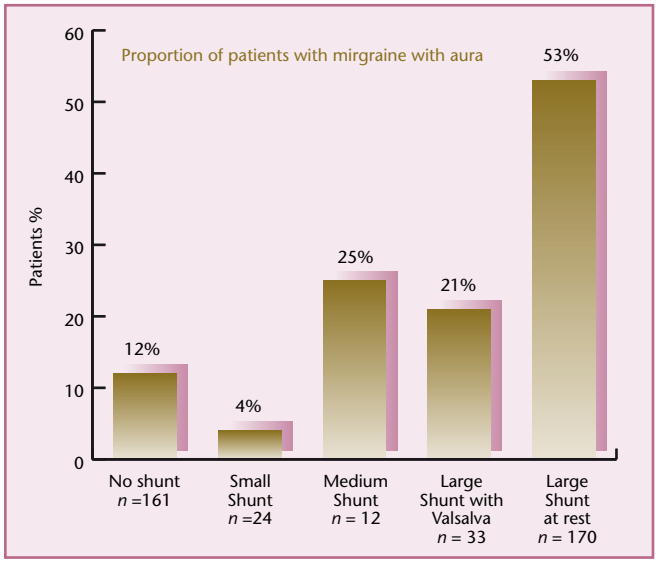

Figure 1. Relationship between size of right-to-left shunt and migraine with aura.[4]

Study	No. patients with migraine	Follow-up duration	Migraine resolution (*n* [%])	Migraine improvement* (*n* [%])
Wilmshurst et al 2000[5]	16 + aura 5 – aura	'Long-term'	7 + aura (43.8%) 3 – aura (60.0%)	15 + aura (93.8%) 3 – aura (60.0%)
Morandi et al 2003[6]	17 ± aura	6 months	5 (29.4%)	15 (88.2%)
Sztajzel et al 2002[7]	15 + aura	13 months	7 (46.7%)	ND
Post et al 2004[8]	12 + aura 14 – aura	≥ 6 months	9 + aura (75.0%) 8 – aura (57.1%)	ND
Reisman et al 2005[9]	50 ± aura 38 + aura 12 – aura	37 weeks	28 ± aura (56.0%) 21 + aura (54.0%) 7 – aura (62.0%)	35 ± aura (70.0%) 26 + aura (68.0%) 8 – aura (67.0%)
Arzabal et al 2005[10]	37 ± aura	3 months	60% ± aura 75% + aura 31% – aura	76% ± aura ND ND
Kimmelstiel et al 2005[11]	24 ± aura	3 months	ND	20 (83.3%)
Sorensen et al 2005[12]	176 ± aura	3 months	153 (86.9%)	ND

* Resolution or improvement; ND = no data

Table 1. Summary of data on migraine improvement in patients with stroke or decompression sickness being treated with PFO closure.[5–12]

Overall, PFO closure was very effective in improving migraine. For migraine with aura, 44–87% of patients reported resolution of attacks after treatment, while 68–94% reported resolution or improvement. Migraine without aura was also improved, but to a lesser extent (31–62% of patients with resolution and 60–67% resolved or improved). One small, prospective case-control study in 24 patients indicated that PFO closure was much more effective than conventional medical treatments in treating migraine, in patients with both migraine and a PFO.[13] Overall, very low adverse event rates were found when closures were conducted by experienced cardiologists.

While the results with PFO closure are promising, the data have several deficiencies. Studies were small and usually retrospective, uncontrolled, and conducted in highly selected populations of patients. They only provide Grade B evidence of clinical effectiveness. The MIST Trial was designed to provide Grade A clinical evidence on the efficacy of PFO closure for patients having migraine with aura.

Progress with the MIST Trial

The MIST Trial design (Figure 2) has several key features necessary for a Grade A clinical trial:

- The trial is large, prospective, randomised, multicentre, double-blind and placebo-controlled.
- The patient group has migraine with aura that is frequent, severe and refractory to treatment.
- A 'sham procedure' placebo group is included to ensure high scientific integrity.
- Analysis is conducted in a specified time period after operation.
- The endpoints are rigorous and clinically meaningful.

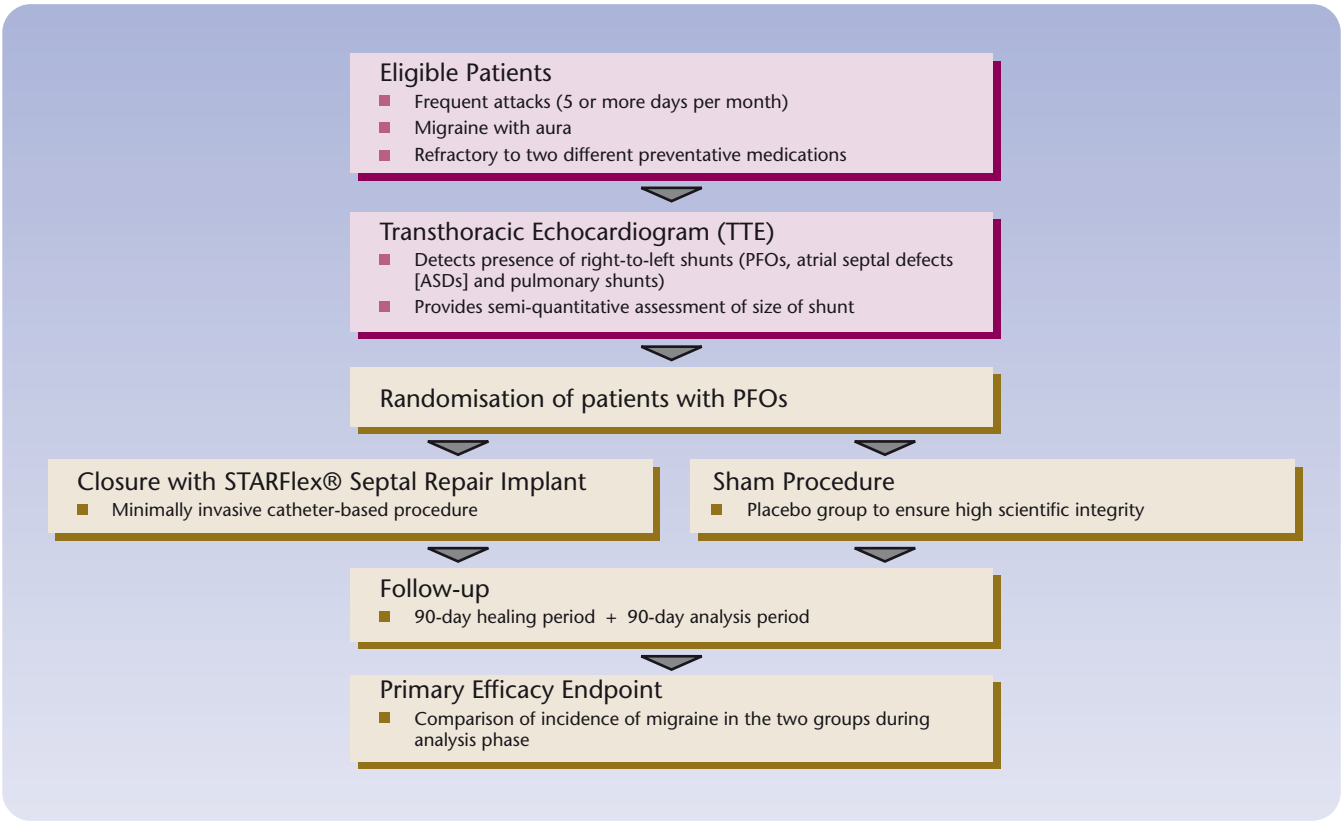

Figure 2. MIST Trial design.

The MIST Trial is currently ongoing and is still blinded. Full results are expected during Spring 2006. However, results from the first 432 patients screened are available for the distribution of right-to-left shunts obtained at the TTE procedure (Figure 3):[14]

- About 60% of patients had shunts, with almost 40% having large PFOs.
- Small shunts were seen in a smaller subgroup of patients (17%).
- Large pulmonary shunts and ASDs were uncommon (5% and < 1%, respectively).

Of the patients with a large PFO, 73 were randomised to the sham placebo procedure and 74 to PFO closure. Results from the sham and closure arms of the MIST Trial will become available in the Spring of 2006.

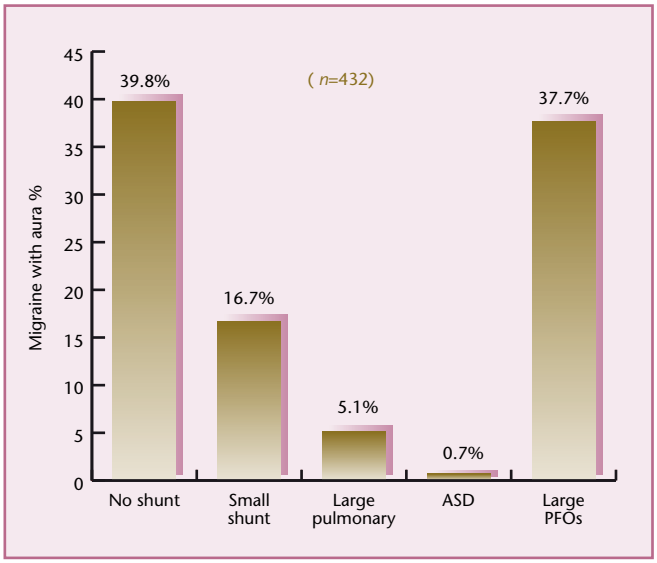

Figure 3. Prevalence and type of right-to-left shunts in patients having migraine with aura in the MIST Trial.[14]

Similar results were reported in a smaller case-control study of patients having migraine with aura compared with healthy controls (Figure 4).[15] Almost half of the migraine patients had a PFO, and almost 40% a moderate-to-large shunt. Compared with the controls, significantly more migraine patients had PFOs and moderate-to-large, but not small, shunts.

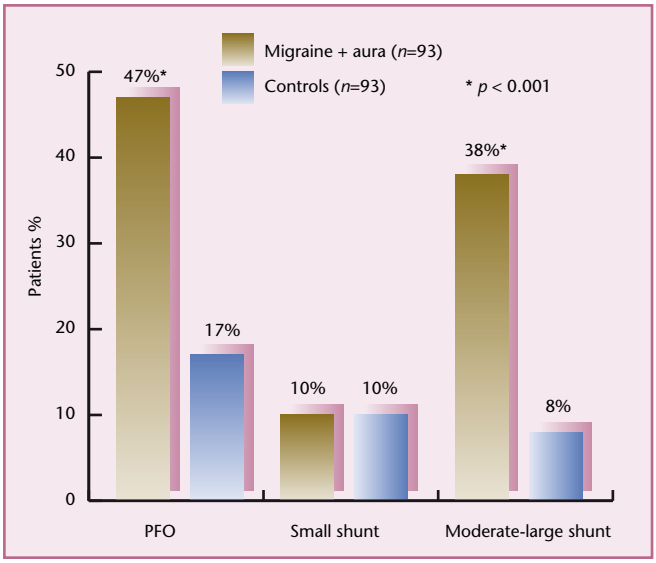

Figure 4. Prevalence and type of right-to-left shunts in a case-control study of patients having migraine with aura compared with healthy controls.[15]

Conclusions

- Prospective studies demonstrate that right-to-left shunts (mostly PFOs) are common in patients with migraine, particularly migraine with aura, and perhaps also in those with cluster headache.[16] In the MIST Trial population, the prevalence of large PFOs is about 6-fold greater in those having migraine with aura compared with the general population. Small shunts seem to be no more common in migraine sufferers than in the general population.
- Studies showing resolution or improvement of migraine in patients following PFO closure are encouraging, and counter some sceptical opinion in the headache world.[17] However, the matter will not be resolved till we have final results from the MIST Trial.
- A second trial, MIST II, is a prospective, randomised, multicentre, controlled study conducted in the USA. The double-blinded trial is designed to randomise approximately 600 migraine patients with a PFO to either PFO closure (using the STARFlex® Septal Repair Implant, NMT Medical Inc, USA) or to a control arm. Enrolment was initiated in January 2006.
- MIST III is a planned extension to the original MIST Trial, where patients who received the sham procedure will have the option to have their PFOs closed after unblinding. These patients, and those whose PFOs were closed, will be followed up for an additional 18 months.
- Further information can be obtained from the dedicated MIST website (www.migraine-mist.org).

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